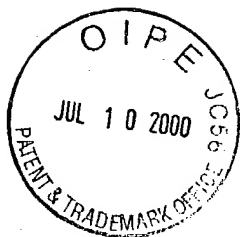


# AUSTRALIA

Patents Act 1990



#12  
1-28

IN THE MATTER OF Australian Patent  
Application Serial No 696764, by Human  
Genome Sciences, Inc.

-and-

IN THE MATTER OF Opposition thereto  
by Ludwig Institute for Cancer Research

## STATUTORY DECLARATION

I, Peter Adrian Walton Rogers of the Department of Obstetrics and Gynaecology, Monash University, Clayton, Victoria, Australia do solemnly and sincerely declare as follows :

### Introduction

- 1.1 I am presently working as Associate Professor and NH&MRC Principal Research Fellow with the Department of Obstetrics and Gynaecology, Monash University, Victoria Australia. Since receiving my Ph.D in 1983, I have worked substantially continuously as a scientific researcher in the U.K. and in Australia in areas of cellular and molecular biology. My research has included substantial studies and explorations in fields of microvascular function, vascular endothelial growth factors, growth of endothelial cells on vascular grafts, tumor angiogenesis, and other areas related to angiogenesis. In addition to my own research efforts and my collaborations with others, I receive numerous invitations to speak at national and international symposiums in these fields of study, I supervise post-graduate research of others, and I have authored and co-authored numerous original research articles published in peer-reviewed journals. My detailed *curriculum vitae* is attached hereto as Exhibit 1.
- 1.2 I have been asked by the Ludwig Institute for Cancer Research ("Ludwig Institute") to serve as a scientific expert in connection with Ludwig Institute's opposition to the issuance of a patent to Human Genome Sciences, Inc., ("HGS") based on HGS's

Australian Patent Application No. 696764. The patent application relates generally to a gene and protein for an alleged novel vascular endothelial growth factor called "Vascular Endothelial Growth Factor 2" ("VEGF2"), and thus pertains to an area of biology closely related to my research and expertise. I understand that Ludwig Institute is a named co-applicant for a different patent application directed to subject matter that may be related to "VEGF2."

1.3 Ludwig Institute has explained to me that it has retained me for the purpose of providing expert scientific analysis of Australian Patent Application No. 696764, as well as related literature, both past and contemporaneous, that may be relevant to the patentability of claims in the application. Ludwig Institute is compensating me for the time that I devote to providing my expert scientific analysis. However, I understand that I have an overriding duty to the Patent Office (and to any Australian Federal Court that should review the Patent Office decision) to provide objective scientific analysis that I believe to be truthful. I hereby affirm that, to the best of my knowledge and belief, factual statements herein are true and opinion statements herein represent my objective scientific opinion and analysis.

1.4 Throughout this declaration, I may refer to Australian Patent Application No. 696764 using various terms such as "the opposed application," "the opposed patent," "the HGS patent" or "the HGS application." All such terms should be understood to refer to the same document. References to the "specification" should be understood as references to the descriptive portion of the application, including text and figures.

1.5 At the time that I execute this declaration in the year 2000, there has been a significant body of published literature relating to the structure and functions of the gene and protein which the opposed patent refers to and I will refer to as "VEGF2." It is a complex protein that undergoes many stages of processing, and that appears to act as a growth factor for the vessels of the lymphatic system that convey lymph from tissues back into the blood. From my review of the file history of the opposed application, I observed little or no mention or appreciation by the Patent Office of any of the developments that occurred after HGS filed its priority application. I think it would

be helpful to the reader of this declaration to provide some context for the gene and protein of the invention that is not available from reading the opposed application or its file history, but that may be relevant to the issues that I discuss below in this declaration in detail.

1.5.1 There is general agreement from at least three different research groups, including HGS, that the human gene which encodes "VEGF2" encodes a polypeptide that is 419 amino acids in length. (See paragraphs 4.11 - 4.11.1, below.) Other research groups that independently discovered the "VEGF2" gene accorded it different names, such as "VEGF-C" or "VRP" (for VEGF-Related Protein). (*Id.*) Most of the investigative reports that are published in respected scientific journals use these other names, especially "VEGF-C".

1.5.1.1 The opposed application does not teach or suggest the complete 419 codon polynucleotide sequence or 419 amino acid polypeptide sequence. Rather, the opposed application teaches a partial sequence of about 350 codons/amino acids. The first (amino-terminal) approximately 69 codons from the full-length VEGF2 sequence are missing in the opposed application. Some time after HGS's scientists eventually discovered the additional 69 amino acids, HGS filed another series of patent applications describing this discovery. (See, *e.g.*, **Documents D44-D46.**) I understand that the Australian Patent Office very recently published its intention to grant some claims in the Australian version of this second series of patent applications. (See Australian Patent Application No. 60467/96, corresponding to Acceptance Serial No. 714484.)

1.5.1.2 It may be of interest that HGS has also filed a third series of patent applications relating to VEGF2 in 1998-1999, including a third PCT application (**Document D86**) that was published in

1999 and that appears to build upon its 1994-1995 first series of applications and 1995-1996 second series of applications.

- 1.5.2. All three independent research groups identified above agree that the "VEGF2" gene encodes a secreted growth factor polypeptide. All polypeptides, even polypeptides such as growth factors that are destined for extracellular secretion, are first synthesized in the cellular cytoplasm. Polypeptides that are destined for secretion generally include a short "signal peptide" at their amino terminus that is usually cleaved off but serves as a vital signal to direct the nascent protein into the cell's protein secretion apparatus. Scientific experiments reported in a respected scientific journal have indicated that the first approximately 31 amino acids from the 419 amino acid form of VEGF2 serve as a signal peptide. (See discussion in paragraph 4.11.1.2, below, and the footnote thereto.) I have seen no comparable published data evincing that the 350 amino acid partial VEGF2 sequence described in the opposed application contains any functional signal peptide, and I would be surprised if it did. It would be unusual for a gene to encode a protein having an alternative start codon and signal sequence 69 codons downstream from a first start codon and signal sequence.
- 1.5.3 Reports in respected scientific periodicals indicate that the processing of "VEGF2" (VEGF-C) is not limited to the mere removal of a 31 amino acid signal peptide. Rather, extensive proteolytic processing occurs at both the amino- and carboxyl-terminal ends of the polypeptide, resulting in a much smaller circulating polypeptide that has enhanced and/or new biological activities relative to the larger pre-processed forms from which it was derived. (See discussion in paragraph 4.11.1.3 below, and documents cited therein.) In its third series of VEGF2 patent applications, HGS acknowledges that such processing occurs. (See, *e.g.*, **Document D86** at p. 17, first paragraph.) However, in the opposed application filed in 1994, there is no evidence presented of complex proteolytic processing.

1.5.4 According to investigative reports published in respected scientific journals, one of the most important activities of the circulating (processed) forms of "VEGF2" (VEGF-C) is that of a growth factor for the vessels of the lymphatic system. See, *e.g.*, **Document D74** (Kukk et al, 1996). See also Jeltsch *et al.*, *Science*, 276: 1423-1425 (1997). The opposed application contains no data from any activity studies that were performed with "VEGF2" and contains no mention of this lymphatic growth factor activity.

### **Lack of Novelty of claims of the Opposed Application**

#### **A. Introduction**

2.1 Through my involvement in this matter, I understand that the claims of a patent define the scope of the invention protected by the patent, and that a patent may only claim novel subject matter: patent claims that encompass subject matter that was described in other patents, publications, or other "prior art" that existed at the time of the effective filing date of the patent claim are invalid. It is my understanding that the effective filing date of a patent is the actual filing date, or sometimes the filing date of a priority application identified by the patent, if the priority application provides support for the claim. Claims that include prior art subject matter within their scope lack novelty, and are said to be "anticipated" by the prior art.

2.1.1 In this section of my declaration, I provide an analysis of whether claims in the opposed application encompass within their scope subject matter that had been described in the literature prior to 08 March 1994, the priority date of the opposed application.

2.1.2 I have reviewed the specification and claims of the opposed application, the written prosecution history of the opposed application in the Australian patent Office, and related prior art. To the extent that the scope of the claims can be determined at all,<sup>1</sup> I have determined that at least patent claims 1-4, 13-28, and 34-61 include within their scope subject matter that was described in the prior

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<sup>1</sup> As set forth below in the section titled "Lack of Clarity," many of the claims lack clarity. (See paragraphs 6.1-6.11.)

art before the earliest claimed priority date (08 March 1994). My detailed analysis follows. In paragraphs 2.2-2.5 I analyze the meaning of certain terminology that appears in many of the claims. Then, in paragraphs 2.6-2.7.22, I analyze the relationship of individual claims and prior art subject matter.

**B. Analysis of the meaning and scope of limitations found in the claims of the opposed application.**

2.2 Several claims in the opposed application are directed to a "fragment, analogue or derivative" of a VEGF2 polypeptide (*e.g.*, claim 28) or to a polynucleotide encoding a "fragment, analogue or derivative" of a VEGF2 polypeptide (*e.g.*, claims 1-4, 21).<sup>2</sup> According to the specification, fragments, derivatives, or analogues may be VEGF2 polypeptides modified such that one or more of the amino acid residues of VEGF2 are substituted with conserved or non-conserved amino acid residues, and/or ones in which additional amino acids are fused to the mature polypeptide. (See, *e.g.*, opposed application at pp. 9-10.) Also, polypeptides resulting from deletion of amino acids would still fall within the commonly accepted definition of "fragment, analogue, or derivative." (See also opposed application at page 7, discussing "deletion variants, substitution variants, and addition or insertion variants.")

2.2.1 The prior art discloses polypeptides (*e.g.*, Vascular Endothelial Growth Factor (VEGF), Placenta Growth Factor (PIGF), and Platelet Derived Growth Factor (PDGF)) having some amino acids that are identical to the VEGF2 that is taught in the specification and some amino acids that are different, as well as polynucleotides encoding such polypeptides. (See, *e.g.*, **Documents D5** (p. 696 Fig. 1 and p. 697 Fig. 2), **D6** (p. 523 Fig. 1 and p. 524 Fig. 3), **D12**, **D18**, **D19** (p. 9269 Fig. 1 and 2), and **D34-D36**.) The relationship between the amino acid sequences of VEGF2 and human PDGF-a, PDGF-b, and VEGF

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<sup>2</sup> Many of the claims are "dependent" claims because they make reference to earlier claims. From my involvement in this proceeding I understand that a claim which makes reference to an earlier claim is interpreted as including all of the limitations of the earlier claim. A claim that makes reference to multiple claims includes the limitations of any one of those other claims (in the alternative).

from the prior art is clearly evident in Figure 2A-2B of the opposed application and summarized in Figure 3.

2.2.2 By changing the "different" amino acids of VEGF2 (by fragmenting, substituting with conserved or non-conserved amino acids, or adding amino acids) one can arrive at a "fragment, analogue, or derivative" of VEGF2 that has an amino acid sequence that is identical to VEGF, PlGF, or a PDGF sequence. In other words, all of the differences between the VEGF2 sequence and prior art sequences such as the human VEGF sequence can properly be characterized as modifications that involved substituting, adding, or deleting residues, the same types of modifications taught in the opposed application for making fragments, analogues, or derivatives. A substantial number of amino acid changes are required to change the VEGF2 sequence into, *e.g.*, the VEGF or PDGF sequences shown in Fig. 2A-2B. However, I find no limitation in the specification or the claims setting a maximum number of modifications that may be performed to generate a "fragment, analogue, or derivative" within the scope of the claim. Thus, polypeptide and polynucleotide claims which recite "fragment," or "analogue," or "derivative" effectively encompass prior art polypeptides and polynucleotides, including but not limited to VEGF, PlGF, and PDGFa and PDGFb polypeptides and polynucleotides.

2.3 Although the claims and specification place no limitation on the number of modifications that may be performed to generate a VEGF2 fragment, analogue, or derivative within the scope of the claim, many of the claims do place the limitation that the fragment, analogue, or derivative be an "active" one (*e.g.*, claims 1-4, 28). Other claims also include a "VEGF2 biological activity" limitation (*e.g.*, claims 13-15, 34-39). For the reasons set forth below, such "activity" limitations, to the extent their meaning can be determined at all,<sup>3</sup> does not exclude prior art VEGF, PlGF, or PDGF polypeptides.

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<sup>3</sup> I find no description whatsoever in the opposed application of any scientific experiment that demonstrates a biological activity for VEGF2. The indefiniteness of this term is discussed below in the section devoted to Lack of Clarity. (See paragraphs 6.5-6.6, below.)

2.3.1 I have carefully reviewed the entire patent specification to attempt to determine the meaning of VEGF2 "activity." The specification appears to provide no explicit definition of VEGF2 activity.

2.3.2 The Examples in the opposed application do not provide any demonstration of a VEGF2 biological activity or any guidance as to VEGF2 biological activity.

2.3.2.1 Example 1 describes a Northern blot analysis ("Northern hybridization") that the inventors performed to examine the levels of expression of VEGF2 in human tissues.<sup>4</sup> Northern hybridizations provide information about the presence, size, and/or quantity of RNA (a nucleic acid) in cells. The RNA may or may not encode a protein. However, a Northern hybridization provides no information about the activity of an encoded protein.

2.3.2.2 Example 2 describes "in vitro transcription and translation" of the VEGF2 cDNA. *In vitro* transcription and translation are processes of making mRNA from a DNA template ("transcription") and making protein from an RNA template ("translation"), using appropriate chemical and enzymatic reagents in a test tube ("*in vitro*"). Such experiments provide no information whatsoever about biological activity of the protein that is synthesized. The only data presented in Example 2 is the *size* of the polypeptides that were purportedly produced.

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<sup>4</sup> Other scientific publications relating to the VEGF2 gene, including publications of the applicant Human Genome Sciences and its scientists, suggest to me that the Experimental procedures or results from Example 1 are flawed. (See paragraphs 4.13-4.13.1, below.)



2.3.2.3 Thus, the Examples of the specification, which are the only sections that appear to describe experiments that were actually performed, provide no guidance as to the meaning of VEGF2 "activity."

2.3.3 The specification suggests many alleged "uses" for VEGF2. The listed uses include to heal wounds, including dermal ulcers, pressure sores, venous ulcers, diabetic ulcers, and abdominal wounds; to promote growth of damaged bone, periodontium, or ligament tissue; to promote endothelialization (*e.g.*, in vascular graft surgery); to diagnosis tumors, to provide cancer therapy, to treat burns and injuries where angiogenesis is desired; to repair the damage of myocardial infarction; to culture vascular endothelial cells. (See opposed application at pp. 2, 16-18.) However, the application fails to explicitly indicate the scientific basis for these alleged uses. For example, there is no description of tests that were performed to demonstrate that VEGF2 has a biological activity that is useful in such procedures, and there is no description of any assay to test for VEGF2 biological activity. The absence of working examples or descriptions of activity assays suggests to me that the patent applicants merely predicted their list of "uses" from activities and/or alleged uses of the prior art growth factors VEGF, PDGF, and/or PIGF. For example, the specification teaches that VEGF is a highly specific growth factor for endothelial cells, can promote angiogenesis, and is an important factor in wound healing; whereas PDGF is a major growth factor for connective tissue. See also **Documents D1** (p. 11260), **D12**, **D16**, **D19** (p. 9270-9271, and Fig. 7), **D36** (column 11 line 67-column 13 line 38); and **D41**. Thus, I find the meaning of VEGF2 "activity" to be ambiguous. The only aspects of the application that suggest a meaning for VEGF2 "activity" are sections that speculate VEGF2 possesses activities characteristic of other prior art members of the "VEGF family" such as VEGF and PDGF.

2.3.4 Since the functions for VEGF2 are alleged to be the same as functions for prior art growth factors (*e.g.*, VEGF, PIGF, and PDGF), it follows that

functional claim limitations directed to "VEGF2 activity" do not exclude prior art growth factor polypeptides (or polynucleotides) from the scope of the claims.

2.3.5 Based on my analysis of the meaning of VEGF2 "activity" and the meaning of "fragment, analogue, or derivative," I conclude that the definition of VEGF2 "active fragment, analogue, or derivative" includes within its scope VEGF, PDGF, and/or PlGF polypeptides, because the claims have neither a functional nor a structural limitation that excludes such polypeptides. Likewise, the genus of polynucleotides which encode an active fragment, analogue, or derivative of VEGF2 includes prior art VEGF-, PDGF-, and/or PlGF-encoding polynucleotides.

2.4 Some of the claims directed to polynucleotides or polypeptides include a limitation relating to "hybridizing" to (the complement of) a VEGF2 polynucleotide<sup>5</sup> or portion of a VEGF2 polynucleotide.<sup>6</sup> (See, e.g., claims 16-20, 34-45, and other claims dependent therefrom.) However, the claim limitations directed to polynucleotide hybridization do not serve to distinguish the prior art that discloses VEGF, PlGF, or PDGF polynucleotides and/or polypeptides, because any DNA can hybridize to VEGF2 DNA if the hybridization conditions (e.g., temperature and ionic strength) are sufficiently relaxed. Neither the claims nor the specification require a level of hybridization stringency that would exclude VEGF, PlGF, or PDGF polynucleotides or encoded polypeptides from the scope of the claims. (No minimum level of

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<sup>5</sup> These claims are generally written in groups of 2-4 claims which specify hybridization to either: SEQ ID NO: 1 or its complement, or the cDNA in ATCC Deposit No. 75698, or the complement of human VEGF-2 RNA, but which are otherwise similar to each other. (See, e.g., claims 13-15 or claims 16-18.) The opposed application teaches that ATCC Deposit No. 75698 contains the sequence in SEQ ID NO: 1 (and presumably its complement, assuming a double stranded cDNA was deposited). To the extent the opposed application teaches or suggests anything about the complement of VEGF-2 RNA, it suggests that the complement of the RNA would be identical (for hybridization purposes) to the complement of SEQ ID NO: 1. Thus, I conclude that these groups of claims are attempts to claim the same subject matter with different wording. My analysis with respect to encompassing prior art is the same irrespective of which "hybridizing" sequence is recited.

<sup>6</sup> Claims which recite portions of VEGF2 polynucleotides (e.g., claim 34 and 35 specify portions that appear to be most highly conserved between VEGF2 and prior art polypeptides and polynucleotides. The more highly conserved regions are the regions that are likely to form the most stable hybrids with prior art polynucleotides. Accordingly, my analysis of the scope of "hybridizing" limitations is applicable to the claims which recite portions as well as the claims which recite complete VEGF2 polynucleotides as the hybridization partner.

hybridization stringency is required at all.) Subparagraphs 2.4.1-2.4.3 explain these principles in greater detail.

- 2.4.1 Polynucleotides such as DNA comprise two strands of complementary base pairs that are held together by hydrogen bonds, thereby forming a stable "double helix." A hybridization experiment operates on the principle that dissociated single strands of base pairs (*i.e.*, denatured DNA) will readily "hybridize" to re-form double helices if they are permitted to contact each other under appropriate conditions. Thus, in a typical hybridization experiment, one studies whether a first polynucleotide (sometimes called a probe) contains a base pair sequence that is sufficiently complementary to a second sequence for the probe sequence to "hybridize" (*i.e.*, renature) to the second sequence.
- 2.4.2 Hybridization experiments are typically performed in buffered aqueous solutions containing controlled amounts of salts and other agents. The temperature at which perfectly matched complementary DNA strands will denature in the hybridization buffer solution is called the melting temperature of the DNA. If a hybridization experiment is performed near the melting temperature, then perfect or near-perfect matching (complementarity) of the base sequences is needed for renaturation to occur. Such hybridization conditions are termed "high stringency." However, as the temperature is lowered, chemical equilibrium begins to favor the formation of double-stranded molecules, even if the base pairing is imperfect and "mismatches" exist. In the parlance of molecular biology, imperfect matches will hybridize to each other under conditions of reduced stringency. If the temperature is dropped low enough, DNA strands whose sequences match poorly will begin to hybridize to each other.
- 2.4.3 Hybridization experiments are commonplace in molecular biology, and scientists can exercise considerable control over the stringency of hybridization conditions. See, *e.g.*, Sambrook *et al.* (1989) cited below in paragraph 3.2.2. By manipulation of the hybridization temperature and the

content of the hybridization buffer (especially salt concentration and pH), a scientist can control the level of sequence similarity that is required for his probe sequence to hybridize to his target sequence. Thus, the mere fact that two sequences will hybridize to each other does not necessarily reflect sequence complementarity. One must also know the stringency of the hybridization conditions to predict the relationship of the hybridizing sequences (*i.e.*, to predict the percent mismatch that may exist).

2.5 Some of the claims to polynucleotides and polypeptides include a limitation directed to polypeptides which bind an antibody which binds (or is capable of binding) to VEGF2. (See, *e.g.*, claims 16-20 and 40-45.) At the outset, I observe that these are "theoretical" antibodies, since the opposed application fails to indicate that the inventors actually made any anti-VEGF2 antibodies. VEGF2 includes some "conserved" regions of high amino acid similarity to prior art VEGF, PDGF and PlGF polypeptides. (See, *e.g.*, boxed region of Fig. 2A). From the theoretical universe of all possible antibodies that bind to VEGF2, a molecular biologist with common general knowledge would reasonably expect that some antibodies which bind to these conserved regions (epitopes) of VEGF2 would cross-react, to some extent, with the similar regions in VEGF or PDGF or PlGF. In other words, VEGF, PDGF, and PlGF are polypeptides which bind an antibody that binds (or is capable of binding) to VEGF2. The expected antibody cross-reactivity means that the claim limitation relating to antibody binding does not exclude prior art VEGF or PDGF or PlGF polynucleotides and polypeptides from the scope of claims.

**C. Analysis of individual claims.**

2.6 In this section, I analyze whether individual claims of the opposed application encompass subject matter that was disclosed in the prior art (*e.g.*, the patent documents and journal articles that were published prior to 08 March 1994).

2.7 Each subparagraph below provides an analysis of one or more individual claims with scope sufficiently large to encompass subject matter that had been disclosed in published literature prior to 08 March 1994. The publications to which I refer do not

necessarily disclose the exact VEGF2 nucleotide or deduced amino acid sequence shown in the opposed application. However, as I explain in the preceding paragraphs and individual subparagraphs that follow, the claims at issue are not limited in scope to the exact VEGF2 sequences disclosed in the application, but are much broader:

- 2.7.1 Claim 1 specifies an isolated polynucleotide and includes within its scope polynucleotides that encode active fragments, analogues, or derivatives of VEGF2. As explained above in paragraphs 2.2 - 2.3.5, prior art VEGF, PDGF, and PlGF polypeptides satisfy the structural and functional requirements of the opposed application to be classified as active fragments, analogues, or derivatives of VEGF2. Thus, prior art documents that teach polynucleotides encoding VEGF, PDGF, and PlGF polypeptides anticipate claim 1. Such polynucleotides are described, *e.g.*, in **Documents D5** (p. 696 Fig. 1), **D6** (p. 523 Fig. 1), **D12**, **D18**, **D19** (p. 9269 Fig. 1), and **D34-D36**.
- 2.7.2 Claims 2-4 depend from claim 1 and include an additional limitation specifying that the claimed polynucleotide is DNA, RNA, or genomic DNA.<sup>7</sup> These are all common types of polynucleotides that are specifically exemplified or suggested in the prior art that discloses VEGF, PDGF, and/or PlGF. See, *e.g.*, **Documents D5** (p. 696-698 and Figs. 1 & 3), **D6** (p. 523-526, Figs. 1, 6, 7, 8, 9, and 10), **D20** (p. 925-928 Fig. 1 and 3), and **D34** (p. 11949-11952, Figs. 1, 3, 4, 6, and 7). Thus, claims 2-4 include prior art polynucleotides within their scope.
- 2.7.3 Many of the cited publications teach Northern hybridization and *in situ* studies that demonstrated that RNA isolated from various sources included VEGF, PDGF, or PlGF mRNA. The RNA from these positive Northern hybridization studies is "isolated" (as defined by the opposed application at page 10) and falls within the scope of claim 3.

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<sup>7</sup> Because of the presence of intervening sequences, a genomic DNA is often much larger than a corresponding cDNA. It is worth noting that the opposed application only exemplifies an isolated cDNA, not an isolated VEGF2 RNA or VEGF2 genomic DNA.

2.7.4 Claims 13-15 are directed to polynucleotides that hybridize to a VEGF2-encoding polynucleotide (or the complement thereto) and that encode "a biologically active fragment of VEGF2." I observe that, during the examination period of the opposed application in the Australian Patent Office, the patent applicant argued that "biological activity may include immunogenic activity of the full length protein." (See Response paper dated 05 August 1998, filed by patent applicant.) Immunogenicity is not generally considered to be a "biological activity" of a protein, because the term "biological activity" is generally used to describe the functions of a protein in native host cells or organisms where the protein does not normally cause an antibody response. However, if "biological activity" has the broader meaning represented by the applicant to the Patent Office, then short peptide sequences of 5, 6, 7, or more residues could be considered biologically active fragments of VEGF2, because fragments of this size are generally considered large enough to elicit an immune response. (See, *e.g.*, Harlow *et al.* (1988), cited below in paragraph 3.2.2.) Both VEGF2 and the prior art human VEGF polypeptide contain an identical 7-mer sequence RCGGCCN (see Fig. 2A of the opposed application, boxed region). Polynucleotides that encode VEGF encode this RCGGCCN peptide portion of VEGF. Thus, polynucleotides that encode VEGF satisfy the "encodes VEGF2 or a biologically active fragment of VEGF2" limitation of claims 13-15, if the term "biologically active fragment" is given the meaning alleged by the patent applicant. For the reasons outlined in paragraphs 2.4-2.4.3, above, human VEGF polynucleotides also satisfy the "hybridizes" limitations of these claims. Thus, claims 13-15 are anticipated by prior art documents that disclose VEGF polynucleotides.<sup>8</sup> (See **Documents D6** (p. 523 Fig. 1), **D7** (p. 16319 Fig. 1), **D12**, **D18** (p. 1307 Fig. 1A and 1B), and **D34-D36**.)

2.7.5 Claims 16-18 are directed to an isolated polynucleotide which hybridizes to a VEGF2 polynucleotide and which encodes a polypeptide which binds an antibody capable of

\* The VEGF2 sequence taught in the opposed application also shares at least three 5-mer peptide sequences (PASCG, CVCKR, and KCACE, residues 232-236, 272-276, and 288-292 of SEQ ID NO: 2) that are identical to 5-mer sequences in a Balbiani Ring 3 protein (BR3P) of the prior art. (See **Document D29** (pp. 337-340 Fig. 5).) These peptides may be sufficient to elicit an immune response, in which case prior art polynucleotides encoding BR3P also anticipate claims 13-15.

binding to VEGF2. As explained above in paragraphs 2.4-2.5, polynucleotides which encode VEGF satisfy the hybridizing limitation and encode a polypeptide (VEGF) which satisfies the antibody binding limitation. Thus, claims 16-18 are anticipated by prior art documents that disclose VEGF polynucleotides. (See **Documents D6** (p. 523 Fig. 1), **D7** (p. 16319 Fig. 1), **D12**, **D18** (p. 1307 Fig. 1A and 1B), and **D34-D36**.) Claim 16 also may be anticipated by prior art documents that disclose BR3P polynucleotides. (See footnote to paragraph 2.7.4.)

2.7.6 Claims 19-20 depend from claims 13-18 discussed above, and include an additional limitation specifying that the claimed polynucleotide is DNA or RNA. DNA and RNA are common types of polynucleotides that are specifically exemplified or suggested in the prior art documents that disclose VEGF. See, *e.g.*, **Documents D6** (p. 523, 524-526, Fig. 1 and 6), **D7** (p. 16318-16320, Fig. 1, 3, 5, 6, and 7), **D12**, **D18** (p. 1307-1308, Fig. 1A, 1B, and 2), and **D34-D36**. See also paragraphs 2.7.2-2.7.3. Thus, claims 19-20 are anticipated by prior art documents that disclose VEGF polynucleotides.

2.7.7 Claim 21 depends from claims 1-4 and 13-20 discussed above, and includes an additional limitation specifying that the polynucleotide is fused to a polynucleotide which encodes a "heterologous polypeptide." The idea of "heterologous polypeptide" was apparently intended to embrace peptides such as heterologous leader sequences known to function as a secretory signal peptide, and short tag sequences (*e.g.*, hexahistidine, hemagglutinin) to facilitate purification (see opposed application at pp. 7-8, 9-10, 14). The inclusion of such heterologous sequences in constructs for recombinant expression of proteins was well known by 1994, and is explicitly described or suggested by prior art documents relating to VEGF, PDGF, and/or PlGF. (See, *e.g.*, **Documents D35** (column 25 lines 4-9, column 32, lines 55-57, and column 33 line 66-column 34 line 4) and **D36** (column 36 lines 29-34).) Thus, the scope of claim 21 embraces prior art teachings related to VEGF, PDGF, and/or PlGF.

2.7.8 Claims 22-27 are directed to a vector containing the polynucleotide of claim 1-21, a host cell engineered with the vector, a method of producing polypeptides encoded by

polynucleotides using the host cell, and a method of producing such host cells. The additional limitations of these claims are all directed to conventional molecular biology materials and methods that are used to express polypeptides encoded by polynucleotides. (See documents cited in paragraph 3.2.2, below.) Such vectors, host cells, and methods are explicitly disclosed or suggested by prior art documents that relate to VEGF, PDGF, and/or PIGF. (See, *e.g.*, **Documents D6** (p. 522), **D18** (pp. 1306 and 1308), and **D36** (column 2 lines 14-17, column 15, line 66, to column 20, line 5; Example 8; Example 13; and Fig. 10, described at column 4, line 20-25).) Thus, the additional limitations of claims 22-27 are also taught by the prior art that anticipates claims 1-4 and 13-20, rendering claims 22-27 anticipated.<sup>9</sup>

2.7.9 Claim 28 specifies an isolated or recombinant polypeptide and includes within its scope polypeptides that are active fragments, analogues, or derivatives of VEGF2. As explained above in paragraphs 2.2 - 2.3.5, prior art VEGF, PDGF, and PIGF polypeptides qualify both structurally and functionally as active fragments, analogues, or derivatives of VEGF2. Thus, the scope of claim 28 embraces prior art disclosures of VEGF, PDGF, and PIGF polypeptides. Such polypeptides are described, *e.g.*, in **Documents D5** (p. 696 Fig. 1 and p. 697 Fig. 2), **D6** (p. 523 Fig. 1 and p. 524 Fig. 3), **D12**, **D18**, **D19** (p. 9269 Fig. 1 and 2), and **D34-D36**.

2.7.10 Claim 53 is directed to a pharmaceutical composition comprising the polypeptide of claim 28 and a pharmaceutically acceptable carrier. As examples of the carrier, the specification identifies saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. (See opposed application at p. 19, first paragraph.) Before the 1994 priority date, these substances were commonly used as carriers, and the prior art documents relating to VEGF, PDGF, and/or PIGF explicitly taught or suggested compositions comprising the polypeptides with such carriers. See, *e.g.*, **Documents D35** (column 11 lines 62-64), **D36** (column 12 lines 66-68), and **D41** (column 3 line

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<sup>9</sup> I observe that claims 25-27 all recite "VEGF-2 polypeptide." However, since the claims apparently specify using a vector containing a polynucleotide according to any one of claims 1-21 (many of which are not limited to a particular sequence), it is not clear whether this term is intended to imply a limitation to a particular sequence. Moreover, the term is indefinite. See paragraphs 6.4-6.4.5, below.



51- column 4 line 36). Thus, the scope of claim 53 (like claim 28) embraces prior art disclosures relating to VEGF, PDGF, and/or PlGF.

2.7.11 Claims 34-39 are directed to an isolated or recombinant polypeptide which has VEGF2 biological activity and which comprises an amino acid sequence that is encoded by a polynucleotide that hybridizes to a VEGF2 polynucleotide or fragment thereof.<sup>10</sup> As explained above in paragraphs 2.3 - 2.3.5, VEGF, PDGF, and PlGF polypeptides described in the prior art possess "VEGF2 biological activity." As explained in paragraphs 2.4-2.4.3, the polynucleotides that encode VEGF, PDGF, and PlGF hybridize to the VEGF2 polynucleotides or fragments thereof recited in the claims. Thus, claims 34-39 are anticipated by prior art documents that disclose VEGF, PDGF, and/or PlGF polypeptides. (See, *e.g.*, **Documents D5** (p. 696 Fig. 1 and p. 697 Fig. 2), **D6** (p. 523 Fig. 1 and p. 524 Fig. 3), **D12, D18, D19** (p. 9269 Fig. 1 and 2), and **D34-D36**.)

2.7.12 Claims 40-45 are directed to an isolated or recombinant polypeptide which (a) comprises an amino acid sequence that is encoded by a polynucleotide that hybridizes to a VEGF2 polynucleotide or fragment thereof; and (b) binds an antibody which binds to VEGF2. As explained above in paragraphs 2.4-2.4.3, prior art polynucleotides that encode prior art VEGF polypeptides (or BR3P polypeptides) will hybridize to the VEGF2 polynucleotides or fragments thereof recited in the claims. As explained in paragraphs 2.5 and 2.7.4, VEGF (and probably BR3P) polypeptides described in the prior art bind antibodies which bind to VEGF2. Thus, VEGF polypeptides (and BR3P polypeptides) satisfy all of the limitations of claims 40-45, so these claims are anticipated by prior art documents that disclose VEGF (and BR3P) polypeptides. (See, *e.g.*, **Documents D6** (p. 523 Fig. 1 and p. 524 Fig. 3), **D12, D18** (p. 1307 Fig 1A and 1B, and p. 1308 Fig. 3), **D29** (p. 337-340 Fig. 5), and **D34-D36**.)

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<sup>10</sup> For the purposes of prior art analysis (both novelty and inventive step), I have assumed that ATCC Deposit No. 97149 (referred to in claims 38 and 44) contains a VEGF2 cDNA. The specification of the opposed application makes no mention whatsoever of this deposit. However, a different patent application filed by the same patent applicant (Human Genome Sciences) describes ATCC Deposit No. 97149 as containing a VEGF2 cDNA. See U.S. Patent Application Serial No. 08/465,968 filed June 6, 1995 (**Document D45**), which was amended prior to issuance to contain a cross reference to ATCC 97149 (see **Document D85**, U.S. Patent No. 5,932,540). I observe from the issued U.S. patent that ATCC 97149 was not deposited with the ATCC until May 12, 1995, more than a year *after* the filing date of the opposed application.

2.7.13 Claim 46 depends from any of claims 28-45 and further includes a limitation specifying that the polypeptide is fused to a heterologous polypeptide. For the reasons discussed above in paragraph 2.7.7 with respect to claim 21, this claim also is anticipated by the prior art. (See, *e.g.*, **Documents D35** (column 25 lines 4-9, column 32, lines 55-57, and column 33 line 66-column 34 line 4) and **D36** (column 36 lines 29-34).)

2.7.14 Claim 47 depends from any of claims 28-46 and contains a further limitation specifying that the polypeptide is in the form of a homodimer. A homodimer is an association of two identical polypeptides. The prior art relating to VEGF that anticipates one or more of claims 28-46 explicitly teaches or suggests that VEGF forms homodimers. (See, *e.g.*, **Documents D12** (p. 22), **D18** (p. 1307-1308), and **D36** (column 10, lines 15-20; column 38, lines 64-66; and column 45, lines 53-56).) In fact, the specification of the opposed application explicitly states that both PDGF- $\alpha$  and PDGF- $\beta$  form either heterodimers or homodimers, and VEGF forms homodimers. (See p. 23, last paragraph.) Thus, claim 47 (like claim 28) embraces prior art that teaches homodimeric forms of VEGF and PDGF polypeptides.

2.7.15 Claim 48 depends from any of claims 28-46 and contains a further limitation specifying that the polypeptide is "glycosylated." Glycosylation of polypeptides (*i.e.*, the attachment of carbohydrate moieties) is commonplace in animals. The prior art relating to VEGF, PDGF, and/or PlGF that anticipates one or more of claims 28-46 explicitly teaches or suggests that these polypeptides are glycosylated. (See *e.g.*, **Documents D12** (p. 22), **D19** (p. 9267, 9269-70, Fig. 3, and Fig. 4), and **D36** (column 10 lines 20-22 and column 45 lines 11-59).) Thus, claim 48 (like claim 28) embraces prior art disclosures of glycosylated forms of VEGF, PDGF, and/or PlGF polypeptides.

2.7.16 Claim 49 is directed to an antibody capable of binding to polypeptides of any of claims 28-48. As explained in paragraphs 2.7.9-2.7.15, one or more of claims 28-48 include VEGF or PDGF or PlGF polypeptides within their scope. Consequently,

claim 49 includes within its scope prior art disclosures of antibodies raised against VEGF or PDGF or PlGF polypeptides. Such antibodies are explicitly disclosed or suggested in **Documents D6** (p. 522 and 524), **D16** (p. 250), **D19** (p. 9268, 9269, and Fig. 3), **D36** (column 14 line 9-39), and **D39** (column 5 line 64-column 6 line 33, and column 13 line 15-50). Thus, claim 49 also is anticipated by the prior art.

2.7.16.1 Claim 55 is similar to claim 49 in reciting an antibody. However, the antibody of claim 55 is an antibody produced by a process of administering a polypeptide according to claim 15 or an immunogenic fragment thereof to an animal and isolating an antibody produced by the animal. At the outset, I find claim 55 lacks clarity because claim 15 is directed to a polynucleotide, and not a polypeptide. However, for the purposes of this analysis, I shall interpret claim 55 as meaning a polypeptide encoded by a polynucleotide of claim 15. As explained above in paragraph 2.7.4, claim 15 is sufficiently broad that it includes polynucleotides that encode VEGF polypeptides. The method steps recited in claim 55 involve the most conventional and well-known method of making antibodies. (See, *e.g.*, Harlow et al., *Antibodies, a Laboratory Manual*, Cold Spring Harbor, New York: Cold Spring Harbor Laboratory Press (1988) cited below in paragraph 3.2.2.) Thus, I find that the antibodies of claim 55 also are anticipated by prior art relating to VEGF. See **Documents D6** (pp. 522 and 524), **D7** (pp. 16318, 16319, and Fig. 4), and **D36** (column 14 lines 9-38 and column 15, lines 31-54).

2.7.17 Claim 50 is directed to an antagonist specific for the polypeptide of any one of claims 28-48. As explained in paragraphs 2.7.9-2.7.15, one or more of these polypeptide claims include VEGF or PDGF or PlGF polypeptides within their scope. Consequently, claim 50 includes prior art disclosures of VEGF or PDGF or PlGF antagonists within its scope. Exemplary antagonists would include antibodies to

VEGF, PDGF, or PlGF.<sup>11</sup> Such antibodies are explicitly disclosed or suggested in **Documents D6** (pp. 522 and 524), **D16** (p. 250), **D19** (pp. 9268, 9269, and Fig. 3), and **D36** (column 14 line 39-column 15 line 30), for example. Thus, claim 50, like claim 49, embraces prior art disclosures of antibodies to VEGF, PDGF, and/or PlGF.

2.7.18 Assuming *arguendo* that VEGF2 as taught in the specification possesses any biological activity that is mediated through cell surface receptors, the claims directed to antagonists of VEGF2 are not novel over prior art disclosures of forms of the receptors to which VEGF2 could bind, but could not signal.<sup>12</sup> See **Document D27** (disclosing a dominant negative Flk-1 protein).

2.7.19 Claims 51 and 52 are directed to a method of treatment of a patient having need of VEGF2 or need to inhibit VEGF2 by administering an effective amount of a polypeptide according to claim 28 or an antagonist against a polypeptide of claim 28. As set forth in paragraphs 2.7.9 and 2.7.17, above, the prior art teaches polypeptides, such as VEGF, within the scope of claim 28 and also antagonists to such polypeptides. Likewise, the prior art contemplates treatment of patients with these polypeptides or antagonists. See, e.g., **Documents D35** (column 10, line 63 to column 12, line 34, and Example 13), **D36** (column 11, line 67 to column 13, line 38, column 14, lines 9-38, and Example 10), and **D41**. As explained above in paragraphs 2.3-2.3.5, the opposed application alleges that the biological activities of VEGF2 are the same as the activities of prior art VEGF or PDGF polypeptides. Because of this alleged equivalence of activities taught in the opposed application, patients in need of VEGF2 (or in need of inhibiting VEGF2) would be treatable with VEGF (or with VEGF antagonists). Consequently, claims 51 and 52 embrace any prior art method of

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<sup>11</sup> The specification of the opposed application explicitly states that an antagonist of a polypeptide could be an antibody against the polypeptide. (See page 24, middle paragraph.)

<sup>12</sup> The opposed application does not teach the full length polynucleotide that encodes VEGF2 or demonstrate that VEGF2 has any "biological activity" (as that term is commonly used). However, the full-length gene from which the VEGF2 cDNA was apparently derived produces a polypeptide which binds to two receptors that were disclosed in the prior art literature. [See, e.g., **Documents D26**, **D28**, and **D33** (describing the Flt4 and Flk1/kdr receptors); see also **Document D70** (teaching that VEGF-C is a ligand for Flt4 and kdr)] **Document D27** discloses a prior art "dominant negative" form of the Flk-1 receptor, which would presumably function as an antagonist of Flk-1-mediated VEGF2 biological activities. Thus, if VEGF2 possesses Flk-1-mediated biological activities, **Document D27** anticipates a claim to VEGF2 antagonist molecules.

treatment of patients with VEGF polypeptides that are encompassed by claim 28 (or prior art method of treatment with VEGF antagonists). In other words, the prior art documents cited above disclosed or suggested the patient population recited at the beginning of claims 51 and 52, and disclosed or suggested treating the patients with a VEGF polypeptides within the scope of claim 28 or antagonist of a VEGF polypeptide. Thus, claims 51 and 52 are not novel and/or describe what was clearly suggested by the prior art.

2.7.20 Claim 56 is directed to a fragment, analogue, or derivative of the polypeptide shown in Figure 1 having an inhibitory activity against the polypeptide of claim 28. At the outset, I observe that the opposed application fails to identify with particularity any fragment, analogue, or derivative of the Figure 1 polypeptide which has an inhibitory activity. As explained above in paragraphs 2.2 - 2.3.5 and 2.7.9, claim 28 embraces prior art polypeptides such as VEGF and PDGF's, and so does the term "fragment, analogue, or derivative of the polypeptide shown in Figure 1." The prior art taught fragments, analogues, or derivatives of VEGF/PDGF that acted as inhibitors. See, *e.g.*, **Documents D16** (p. 250) and **D36** (column 13 line 61-column 14 line 8). Thus, the prior art anticipates claim 56.

2.7.21 Claims 57-61 are omnibus claims that make reference to previous claims discussed above and also to "the Figures and/or Examples." As explained above, the claims referred to stand anticipated by prior art, such as prior art relating to VEGF and PDGF's. Since the Figures also disclose VEGF and PDGF's (See, *e.g.*, Figures 2A-2B), I find that this reference to the Figures does not serve to exclude the prior art, and claims 57-61 are also anticipated.

2.7.22 In the preceding paragraphs I cite to various documents, but these should not be considered to be the only documents that disclose the subject matter of particular claims. Other documents from **Documents D1-D41** and **D78** may disclose the same subject matter, and documents that I have not cited may disclose the same subject matter.

#### D. Conclusion

- 2.8 For the reasons outlined above, it is my opinion that all of the claims 1-4, 13-28, 34-53, and 55-61 are anticipated by the prior art.

### **Lack of Inventive Step**

#### **A. Introduction**

- 3.1 Through my involvement in this matter it is my understanding that Australian patent law requires that, for an invention to be patentable, it must not only be novel over the prior art, but it must have an "inventive step" compared to the common general knowledge in Australia before the priority date and compared against each individual, publicly available document when read in light of the common general knowledge. If patent claims embrace subject matter that is a routine and obvious variation of what was taught in an individual prior art document, then the patent claim lacks inventive step.

- 3.2 I believe that my background and experience, as outlined above, provides me with an understanding of the common general knowledge in the fields of the invention, in Australia, at the time that the U.S. priority application and the opposed Australian (PCT) application were filed.

- 3.2.1 The relevant common general knowledge is the common general knowledge of an individual with an advanced degree (*e.g.*, Ph.D and/or M.D.), such as an individual being exemplified by biochemists, protein and/or polypeptide biochemists, molecular biologists, and/or cell biologists, or teams of biochemists, protein and/or polypeptide biochemists, molecular biologists, and/or cell biologists, involved in the isolation and characterization of nucleic acid sequences, automated or manual nucleic acid sequencing methods, performing and interpreting searches of publicly available databases for sequences displaying homology to a query sequence, transformation of prokaryotic and eukaryotic organisms with isolated nucleic acid sequences, expression of heterologous sequences in prokaryotic and eukaryotic host cells and/or organisms, isolation and/or characterization of factors involved in cell growth and proliferation, especially but not limited to those factors associated

with angiogenesis, in Australia at or before the priority date of the claims of the opposed application.

3.2.2 The following documents are relevant to my analysis of inventive step in that they all include disclosures concerning general methods in molecular biology and recombinant DNA and antibody technology which form part of the relevant common general knowledge in Australia at or before the priority date of the claims of the opposed application:

Sambrook, J. et al., (1989). Molecular cloning, 2nd Edn. Vols. 1-3. Cold Spring Harbour Laboratory Press, Cold Spring Harbour, New York, USA;

Watson et al. (1983). Recombinant DNA. 1st Edn. Scientific American Books, W.H. Freeman & Co. NY, USA;

Watson et al (1992). Recombinant DNA. 2nd Edn. Scientific American Books, W.H. Freeman & Co., NY, USA;

Lewin, B. (1987). Genes III. John Wiley & Sons, New York, USA;

Stryer, Lubert (1988) Biochemistry, 3rd Edn. W.H. Freeman and Company, New York, USA;

Ausubel, F.A. et al. (1994) Current Protocols in Molecular Biology, John Wiley and Sons, New York, NY, USA;

Harlow et al., Antibodies, a Laboratory Manual, Cold Spring Harbor, New York: Cold Spring Harbor Laboratory Press (1988);

Coligan, J.E. et al (1994) Current Protocols in Immunology, John Wiley and Sons, New York, NY, USA;

Peters, P. (1993) Biotechnology: A Guide to Genetic Engineering, WCB McGraw-Hill, Boston, Massachusetts, USA;

Nicholl, D.S.T. (1994) An Introduction to Genetic Engineering, Cambridge University Press;

Goeddel, D.V. (Ed) (1991) Methods in Enzymology volume 185, Gene Expression Technology, Academic Press;

Gilbert, H.F. (1992) Basic Concepts in Biochemistry: A Student's Survival Guide, McGraw-Hill, Inc.;

3.2.3 For the purposes of this section, I have also considered each of **Documents D1-D41** for what each individual document teaches in light of the common general knowledge in Australia at or before the priority date of the claims of the opposed application (as reflected, for example, in the documents cited in paragraphs 3.2.2.)

3.2.4 Likewise, I find the following documents relevant to my analysis of inventive step:

**Document D79**, Anderson, W.F. (1992) "Human Gene Therapy," *Science*, 256:808-813;

**Document D80**, Friedman, T. (1992) "A Brief History of Gene Therapy," *Nat Genetics*, 2: 93-98

**Document D81**, Williams, R.S. (1993) "Southwestern Internal Medicine Conference: Prospects for Gene Therapy of Ischemic Heart Disease," *Am. J. Med. Sci.*, 306: 129-136;

**Document D82**, Hockel et al. (1993), "Therapeutic Angiogenesis," *Arch. Surg.*, 128: 423-429;

**Document D83**, Guzman et al. (1993), "Efficient Gene Transfer Into Myocardium by Direct Injection of Adenovirus Vectors," *Circ. Res.*, 73: 1202-1207;

3.2.5 The common general knowledge at the time of the filing of the priority application included knowledge of the following:

nucleotide and protein sequence information regarding vascular endothelial growth factor (VEGF), platelet derived growth factors (PDGFs, such as PDGF- $\alpha$  and PDGF- $\beta$ ) and placenta growth factor (PIGF); knowledge of the biological activities of these proteins; and sequence alignments to identify conserved regions of these proteins;



vectors and host cells suitable for recombinant expression of mammalian proteins, and methodologies for producing such proteins recombinantly;

materials and methods for generating short peptides of any desired amino acid sequence synthetically;

materials and methods for selectively altering one or more codons of a gene and using the altered gene to produce proteins with one or more amino acids selectively changed or deleted or added;

materials and methods for making polyclonal and monoclonal antibodies against virtually any purified antigen, including but not limited to purified proteins, recombinant proteins, and synthetic peptides; and

materials and methods for performing gene therapy on human cells or in humans.

3.2.6 The common general knowledge before 1994 included an appreciation that molecules having the apparent biological activities of VEGF or PDGF or PlGF would be useful to treat certain diseases and conditions, and that other diseases and conditions might be effectively treated by inhibiting the apparent biological activities of VEGF or PDGF or PlGF. See, *e.g.*, **Documents D16** (p. 250), and **D36** (column 11, line 67, to column 15, line 54).

3.3 This section of my declaration should be viewed as an extension of the previous section relating to novelty, which is incorporated herein by reference. In the novelty section I focused on what had actually been disclosed in individual prior art documents, such as **Documents D1-D41** and **D78**. In this section, I have been asked to focus not only on what was explicitly disclosed in such documents, but also what was clearly suggested by individual documents to a worker possessed with the

common general knowledge.<sup>13</sup> In addition to (or in the alternative to) lacking novelty, it is my opinion that at least patent claims 1-4, 11, 19-28, 32, 40, 46-54, and 56-61 lack inventive step because they encompass what would have been considered obvious or routine from individual documents and/or from the common general knowledge. My detailed analysis follows:

**B. Analysis of Inventive Step and the claims of the Opposed Application.**

3.4 Claims 1-2, 28, 56-57, and 61, at least, attempt to define an invention pertaining to fragments, analogues, and/or derivatives of VEGF2 that possess VEGF2 activity (or polynucleotides encoding them). As explained in the following subparagraphs, these claims include within their scope subject matter that was obvious or routine from individual prior art documents.

3.4.1 Many individual prior art documents disclosed or suggest one or more of the prior art growth factor genes and proteins (*e.g.*, VEGF, PDGF, and PIGF), or fragments, analogues or derivatives of these prior art growth factors. (See, *e.g.*, documents cited in paragraphs 2.3.3 and 2.7.1-2.7.22.).

3.4.2. As explained in detail above in paragraphs 2.2-2.3.5, the specification of the opposed application fails to distinguish the theoretical structure or activity of VEGF2 fragments, analogues, or derivatives possessing VEGF2 activity from the structure and activity of the prior art growth factors VEGF, PDGF, or PIGF, or fragments, analogues or derivatives of these growth factors that were disclosed or suggested in the prior art. The specification also fails to provide any teaching or exemplification of active fragments, analogues, and/or derivatives of VEGF2. The absence of particular examples and the absence of characteristics to distinguish active VEGF2 fragments, analogues, and derivatives from prior art VEGF, PDGF, PIGF, and fragments thereof lead me to conclude that there is no invention in the opposed application with respect

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<sup>13</sup> In the above section relating to novelty, I sometimes discussed what various documents suggested to the reader. Such discussions should be understood as relating to lack of inventive step.

to "active fragments, analogues, and/or derivatives" of the VEGF2 gene or protein. In other words, I find that VEGF, PDGF, and PlGF, and active fragments, analogues, and/or derivatives thereof were known or suggested by individual prior art documents cited above in paragraphs 2.3.3 and 2.7.1-2.7.22, and that such molecules are within the scope of claims 1-4, 28, 56-57, and 61.

3.4.3 Claims 3 and 4 specify an isolated RNA polynucleotide and an isolated genomic DNA polynucleotide, respectively. As explained above, the scope of claims 3 and 4 are sufficiently broad to encompass isolated RNA/genomic DNA polynucleotides that encode not only VEGF2, but also ones that encode VEGF or PDGF or PlGF. (See, *e.g.*, paragraphs 2.2-2.3.5 and 2.7.1-2.7.2, above.) To the extent that the prior art had not explicitly isolated RNA or genomic DNA encoding any of these three polypeptides, it is my opinion that such RNA and genomic DNA was no more than routine variation over prior art disclosures of cDNAs encoding these three polypeptides. Thus, I find that the subject matter of claims 3 and 4 is nothing more than a routine and obvious extension of individual documents that taught a cDNA polynucleotide that encodes VEGF or PDGF or PlGF. See, *e.g.*, **Documents D5** (p.696, Fig.1), **D6** (p.523, Fig. 1), **D12** (pp. 20-21), **D18** (pp. 1307-1308), **D19** (p.9269, Fig. 1), **D34** (pp. 11948-11950), **D35** (col. 27, line 45, to col. 29, line 24, and Fig. 7), and **D36** (col. 31, line 20, to col. 32, line 68, and Fig. 7).<sup>14</sup>

3.4.4 Claim 21 depends from claim 1 (and other claims) and further specifies that the polynucleotide of claim 1 is fused to a polynucleotide which encodes a

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<sup>14</sup> The opposed application does not actually teach a VEGF2 genomic DNA. Thus, if genomic DNAs for growth factors like VEGF or VEGF2 are not obvious and routine variations from teachings of cDNAs, then it is my opinion that the opposed application fails to provide the public with a disclosure that is insufficient to obtain a genomic VEGF2 DNA as recited in claim 4.

heterologous polypeptide. Similarly, claim 46 depends from claim 28 (and other claims) and further specifies that the recombinant polypeptide of claim 28 is fused to a heterologous polypeptide. I explain above that claims 1 and 28 are sufficiently broad to embrace polynucleotides and polypeptides of prior art growth factors such as VEGF, PDGF, or PIGF. (See, *e.g.*, paragraphs 2.7.1 and 2.7.9, above.) It is my opinion that, prior to the priority date of the opposed application, it was routine to fuse a protein-encoding polynucleotide to heterologous polynucleotide sequences which encoded heterologous polypeptides such as epitopes to facilitate purification. [See, *e.g.*, documents cited in paragraphs 2.7.7 and 3.2.2, above] Thus, the subject matter of claims 21 and 46 is merely a routine and obvious extension over individual prior art documents which taught a cDNA and deduced amino acid sequence for VEGF or PDGF or PIGF. See, *e.g.*, **Documents D5** (p.696, Fig.1), **D6** (p.523, Fig. 1), **D12** (pp. 20-21), **D18** (pp. 1307-1308), **D19** (p.9269, Fig. 1), **D34** (pp. 11948-11950), **D35** (col. 27, line 45, to col. 29, line 24, and Fig. 7), and **D36** (col. 31, line 20, to col. 32, line 68, and Fig. 7).

3.4.5 Claims 47 and 48 depend from claim 28 (as well as other claims) and further include limitations relating to polypeptides that form a homodimer or that are glycosylated. For the reasons specified in paragraphs 2.7.14-2.7.15, it is my opinion that these limitations merely reflect the prior art knowledge that VEGF and/or PDGF polypeptides formed homodimers and were glycosylated. Therefore, the subject matter of claims 47-48 is nothing more than a routine and obvious extension of the prior art documents cited in paragraphs 2.7.14-2.7.15.

3.4.6 Claim 49 specifies an antibody that is capable of binding to a polypeptide according to claim 28 (or other claims). For the reasons set forth in paragraph 2.7.16, I find that the subject matter of claim 49 is disclosed in or is no more than an obvious and routine extension of the individual **Documents D6, D16, D19, D36, and D39** cited therein. Similarly, the subject matter of claim 50, directed to an antagonist, is disclosed in or is no

more than an obvious and routine extension of the teachings of individual documents identified and discussed in paragraphs 2.7.16-2.7.17.

3.4.7 Claim 53 recites a pharmaceutical composition comprising the polypeptide of claim 28 and a pharmaceutically acceptable carrier. For the reasons set forth above in paragraph 2.7.10, the subject matter of this claim is disclosed in or is no more than an obvious and routine extension of the teachings of individual documents cited therein.

3.5 Certain claims (*e.g.*, claims 11, 32, and 40, and claims dependent therefrom) encompass polypeptides (or encoding polynucleotides) that differ from prior art VEGF, PDGF, and/or PlGF polypeptides (and polynucleotides) by as few as three or four amino acids (or codons).<sup>15</sup> Before the 1994 priority date, it was routine for the skilled addressee to introduce 3-4 amino acid (or codon) changes into a polypeptide (or polynucleotide) sequence, *e.g.*, using procedures such as site-directed mutagenesis. [See, *e.g.*, documents cited in paragraph 3.2.2, above.] Thus, in the absence of a noteworthy change in properties that results from the change in 3-4 amino acids, I would conclude that there is nothing inventive in the molecules of claims 11, 32, and 40 over the prior art VEGF, PDGF, and/or PlGF cDNA and polypeptide molecules. (In the absence of a change in function or properties, the molecules of claims 11, 32, and 40 would represent no more than a minor change in structure with no changes in function.) I have reviewed the opposed application and find that the inventors have not alleged or demonstrated that the three or four specified alterations to native PDGF or VEGF cause the encoded proteins to differ in

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<sup>15</sup> These claims recite a short segment of the VEGF2 gene or protein (*e.g.*, residues 61-74 of SEQ ID NO: 2) that contains several residues which are highly conserved when compared to VEGF or PDGF polypeptides. (See boxed portion of Fig. 2A in the opposed application.) These claims also employ the term "comprising" to define their metes and bounds. As I understand the intended meaning of the term "comprising" (patent at page 29, last paragraph), the claim would include the recited core residues 61-74 of SEQ ID NO: 2, in combination with any other residues, including but not limited to all of the upstream and downstream residues of VEGF or PDGF as shown in Figure 2. Thus, by way of example, claim 11 would appear to include a polynucleotide that encoded a polypeptide identical to VEGF, except that codons for the sequence PSCVPLMRCGGCCN in the middle of VEGF would be replaced by codons for the sequence PPCVSVYRCGGCCN, a net change of four codons in the entire VEGF molecule (changes emphasized). A net change of only three codons is needed to arrive at the PDGFa sequence shown in the top line of Fig. 2A of the opposed application.

activity or function from native VEGF, PDGF, and/or PlGF. Thus, I find that polynucleotides and polypeptides within the scope of claims 11, 32, and 40 represent nothing more than routine modifications of individual prior art documents which teach VEGF or PDGF cDNA and deduced amino acid sequences, which modifications result in no reported or apparent unexpected properties. See, *e.g.*, Documents D5 (p.696, Fig.1), D6 (p.523, Fig. 1), D12 (pp. 20-21), D18 (pp. 1307-1308), D34 (pp. 11948-11950), D35 (col. 27, line 45, to col. 29, line 24, and Fig. 7). and D36 (col. 31, line 20, to col. 32, line 68, and Fig. 7).

3.5.1 Claims 19 and 20 depend from claim 11 and specify DNA and RNA polynucleotides, *i.e.*, the two common forms of polynucleotides. The art cited in paragraph 3.5.1 discloses cDNAs, which are DNA. Thus, the subject matter of claim 19 is obvious for the same reasons (set forth in 3.5.1) that the subject matter of claim 11 is obvious. As explained in paragraph 3.4.3, RNA polynucleotides represent a routine variation over DNA polynucleotides. Therefore, because the subject matter of claim 11 is no more than an obvious and routine extension of individual prior art documents, dependent claim 20 also represents no more than an obvious and routine extension of individual prior art documents.

3.6 In the section above pertaining to novelty, I explain that many of the claims which recite polynucleotides or polypeptides are sufficiently broad to encompass VEGF or PDGF or PlGF polynucleotides or polypeptides. I also explain that dependent claims which specify vectors, host cells, methods of producing polypeptides, antibodies, antagonists, and the like (*e.g.*, at least claims 22-27 and 58-60) would include within their scope vectors and host cells that include VEGF or PDGF or PlGF polynucleotides; methods of producing VEGF or PDGF or PlGF polypeptides; and antibodies and antagonists to VEGF or PDGF or PlGF. It was a common practice before the priority date of the opposed application to insert a protein-encoding polynucleotide into a vector and insert the vector into a host cell to attempt to amplify the polynucleotide and/or to recombinantly produce the encoded

polypeptide.<sup>16</sup> [See, *e.g.*, documents cited in paragraph 3.2.2, above.] Thus, even if no single prior art document discloses a vector or host cell containing a VEGF or PDGF or PlGF polynucleotide, or a method of recombinant production, I believe that such materials and methods were no more than routine and obvious variations of the individual documents which disclosed VEGF or PDGF or PlGF DNA or deduced amino acid sequences. Thus, I find that the subject matter of claims 22-27 and 58-60 of the opposed application is disclosed in or is no more than an obvious and routine extension of documents which taught a VEGF or PDGF or PlGF polynucleotide or deduced amino acid sequence. See, *e.g.*, **Documents D5** (p.696, Fig.1), **D6** (p.523, Fig. 1), **D12** (pp. 20-21), **D18** (pp. 1307-1308), **D19** (p.9269, Fig. 1), **D34** (pp. 11948-11950), **D35** (col. 27, line 45, to col. 29, line 24, and Fig. 7), and **D36** (col. 31, line 20, to col. 32, line 68, and Fig. 7).

- 3.7 The common general knowledge and/or the teachings of individual documents before 1994 included an appreciation that molecules having the apparent biological activities of VEGF or PDGF or PlGF would be useful to treat certain diseases and conditions, and that other diseases and conditions might be effectively treated by inhibiting the apparent biological activities of VEGF or PDGF or PlGF. See, *e.g.*, **Documents D16** (p.250), **D35** (column 10 line 63-column 12 line 34, and Example 13), **D36** (column 11 line 67-column 13 line 38, column 14 lines 9-38, and Example 10), and **D41**. Thus, the idea of using VEGF or PDGF or PlGF (or antagonists of these molecules) to treat a patient was within the common general knowledge before 1994, even if actual treatment had not been performed by that date. As explained in paragraph 2.7.19, above, claims 51 and 52 are sufficiently broad to include within their scope treatments using VEGF or PDGF or PlGF (or antagonists of these molecules). Thus, to the extent that such treatment was feasible, it is my opinion

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<sup>16</sup> The opposed application does not actually teach that recombinant, biologically active VEGF2 was actually produced. I find that the claims are obvious because they encompass prior art technology relating to VEGF and PDGF, and I express no opinion at this time whether expression of VEGF2, which apparently had never been performed, would have been routine. If expression of VEGF2 were not routine, then the description of methods of expression of polypeptides found in the opposed application may be insufficient for enabling the reader possessed with the common general knowledge to express VEGF2.

that claims 51-52, directed to such treatment, represent no more than obvious and routine extensions of individual prior art documents.<sup>17</sup>

3.7.1 Claim 54 is similar to claim 51 and further specifies that the therapeutic amount of polypeptide is to be administered via providing the patient with DNA encoding the polypeptide and expressing the polypeptide *in vivo*. In other words, claim 54 is apparently not directed to protein therapy, but rather is directed to "gene therapy." (See paragraph 6.8.1, below.) As explained in paragraph 2.7.19, the scope of claim 51 embraces the administration of prior art VEGF polypeptides, and thus claim 54 embraces gene therapy with prior art VEGF-encoding polynucleotides. Upon review of the opposed application, I find no description of any instances where VEGF2 gene therapy was successfully performed, or even attempted. Also, I find no teachings or guidance relating to performing gene therapy treatment that were not within the common general knowledge in Australia at the time of filing the opposed application. Thus, if obstacles existed in the prior general knowledge relating to generic methods of treatment as claimed,<sup>18</sup> then it is my opinion that the opposed application fails to overcome the obstacles, and therefore the application lacks a disclosure sufficient to practice methods of treatment. If no such obstacles existed, then it is my opinion that the subject matter of claim 54 is nothing more than an obvious extension of teachings of any of the individual documents cited above that disclose a VEGF polynucleotide sequence and teach that VEGF has therapeutic potential in humans.

## C. Conclusion

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<sup>17</sup> Upon review of the opposed application, I find no teachings relating to methods of treatment that were not within the common general knowledge. Thus, if obstacles existed in the prior general knowledge relating to generic methods of treatment as claimed, then it is my opinion that the opposed application fails to overcome the obstacles, and therefore the application lacks a disclosure sufficient to practice methods of treatment. I express no opinion at this time as to whether obstacles, such as uncontrollable and undesirable side effects, existed with efforts to develop therapeutics involving VEGF or VEGF inhibitors.

<sup>18</sup> I express no opinion at this time as to whether obstacles, such as uncontrollable and undesirable side effects, existed with efforts to develop therapeutics involving VEGF or VEGF inhibitors.



- 3.8 For the reasons outlined above, it is my opinion that at least patent claims 1-4, 11, 19-28, 32, 40, 46-54, and 56-61 encompass subject matter that is disclosed in, or represents no more than an obvious and routine extension of, subject matter taught in individual prior art documents.

### **Insufficiency**

#### **A. Introduction**

- 4.1 Through my involvement in this matter, it is my understanding that Australian patent law (Section 40(2)(a)) includes a sufficiency requirement that focuses on whether a specification is sufficient to disclose the method of carrying out the invention to a person reasonably competent in the relevant field of endeavor and equipped with the common general knowledge in that field.

4.1.1 It was explained to me that the evaluation for sufficiency should take into account the common general knowledge in the art, in the sense that gaps in a patent application are not necessarily problematic when the skilled practitioner can fill the gaps with reference to the common general knowledge. At the same time, for sufficiency to exist, further inventive ingenuity should not be required to practice the claimed invention. If a competent person cannot achieve the promised result because of deficiencies in the information given in the specification, there is insufficiency.

4.1.2 I was asked to consider whether the specification of the opposed application included teachings that were commensurate in scope with the claims. It was explained to me that the directions provided in the specification must be sufficient for the execution of the invention throughout the breadth or range of the claims, and that an applicant who chooses to claim an invention broadly has an obligation to make a correspondingly wide disclosure.

4.1.3 It was also explained to me that the sufficiency of an application's disclosure is evaluated as of the application's filing date and/or priority date. If the claimed subject matter is insufficiently supported by the priority application

(e.g., the priority application is non-enabling), then the claims are not entitled to the benefit of the priority date.

4.1.4 It was also explained to me that Australian law requires that a specification must describe the best method known to the applicant of performing the invention at the time of filing of the application. I was asked to consider whether there was any evidence of a violation of this requirement in the opposed application, even though such a determination is difficult without knowledge of what was in the minds of the inventors.

4.2 In this section of my declaration, I provide an analysis of whether the specification of the opposed application contains a disclosure sufficient to practice the claimed invention.

**B. The Priority Date of the HGS Application.**

4.3 I have reviewed the priority application (U.S. Patent Application Serial No. 08/207,550, filed 08 March 1994) cited in the opposed application to analyze whether the priority application contains sufficient subject matter upon which to fairly base claims in the opposed application. As set forth in the next paragraphs, none of claims 1-61 appear to me to be fairly based on, or enabled by, the priority application.

4.3.1 The U.S. priority application fails to identify with particularity any American Type Culture Collection biological deposit. Thus, at least claims 1, 6, 8, 14, 17, 28, 38, and 44, all of which specify a particular biological deposit that is not specified in the priority application, are not enabled by or fairly based on the priority application. (Many other claims depend from this list of claims, and thus would not be fairly based or enabled by the priority application by virtue of their dependency.)

4.3.2 The opposed application specifies that the unidentified ATCC deposit is the "controlling" description of the invention. (See specification at page 9, lines 1-6.) Thus, the failure to identify the deposit constitutes a failure to

sufficiently teach the controlling definition of the invention. Consequently, I would conclude that none of the claims are entitled to the priority date.

**C. The claimed invention is not fully and sufficiently described**

- 4.4 My review of the opposed application and of related documents published by the applicant and inventors *after the filing* date suggests that the specification of the opposed application fails to identify the best method known to the applicant of performing the invention. In particular, the applicant claims "VEGF2" polypeptides and polynucleotides encoding such polypeptides, but extrinsic evidence indicates that the applicant failed to disclose *the complete* VEGF2 polynucleotide and polypeptide sequences in the specification. I incorporate by cross-reference the analysis in paragraphs 4.11-4.11.3 below.
- 4.5 I have no means of determining when the applicants discovered the complete VEGF2 sequence, but if the applicants knew the full length VEGF2 sequence at the time of filing the opposed application, then I would conclude that the opposed application fails to describe the best method of practicing the VEGF2 polynucleotide/polypeptide invention.
- 4.6 It is also my opinion that the opposed application contains an inadequate characterization of VEGF2 "activity." In particular, most of the claims (*e.g.*, claims 1-10, 13-15, 19-30, 34-39, 46-51, and 53-61) attempt to define an invention by reference to VEGF2 activity, yet the specification as a whole fails to provide any evidence of VEGF2 biological activity and fails to provide any working examples to establish that the polypeptides claimed (or encoded by claimed polynucleotides) possess the alleged VEGF2 activity. (See also discussion of VEGF2 activity in paragraphs 2.3-2.3.5 and 6.5-6.6.)
- 4.6.1 Initially, I observe that VEGF2 (having the amino acid sequences set forth in the sequence listing or figures of the opposed application) was purportedly an unknown and uncharacterized protein prior to the filing of the opposed application. If VEGF2 were unknown, then the common general knowledge

would have been devoid of any knowledge of VEGF2 biological activities as of the applicant's filing date or priority date. It was incumbent upon the patent applicant to provide such activities. The fact that the specification fails to demonstrate any VEGF2 biological activity is especially significant in that the biological activities of VEGF2 (if any) is a concept analogous to utility: if one does not know the activities of VEGF2, one would not know how to use VEGF2 (except as a curiosity for further research).

4.6.2 I have reviewed the opposed application carefully, and it contains no demonstration (*e.g.*, data) whatsoever of a VEGF2 biological activity. Since the specification contains about 29 pages of fairly technical text, it may be helpful if I elaborate on this conclusion.

4.6.2.1 Initially, I observe that *very little of the text of the extensive specification is specifically directed to the claimed invention*. Instead, most of the specification comprises general teachings relating to recombinant DNA technology that are no more relevant to VEGF2 than to other human genes and proteins. This fact would be apparent to any reader having common general knowledge of the field of the invention, such as knowledge of general recombinant DNA technology found in the general treatises cited above in paragraph 3.2.2. The fact that most of the specification is not particularly related to VEGF2 also is evident if one performs a comparison of the opposed application to other patent applications filed by the applicant, Human Genome Sciences, on completely different inventions. Such a comparison demonstrates that the VEGF2 specification *primarily* comprises "stock" text that the applicant uses in many of its biotechnology patent

applications without regard to the particular DNA or protein that the applicant claims.<sup>19</sup>

4.6.2.2 The Examples section of the opposed application (pages 27-29) apparently contains data from actual scientific experiments relating specifically to VEGF2. However, as I explained above in paragraphs 2.3.2-2.3.2.3, the examples provide no guidance as to the meaning of VEGF2 "activity."

4.6.2.3 In addition to the "stock" language and the examples, neither of which have any relevance to VEGF2 biological activity, the specification of the opposed application also alleges numerous properties and/or uses for VEGF2.<sup>20</sup> However, there is nothing whatsoever in the application to indicate that these alleged activities are supported by any actual scientific experiments or evidence. The specification fails to demonstrate that VEGF2 possesses any of these activities or is useful for any of the alleged uses. The addressee does not know which alleged activities are correct, or which are

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<sup>19</sup> See, e.g., **Document D47** (International Application No. PCT/US95/02950, filed on 8 March 1995 by Human Genome Sciences, Inc. (WO 95/24414), directed to "Fibroblast Growth Factor-10."); **Document D48** (U.S. Patent No. 5,633,147, filed 08 March 1994, assigned to Human Genome Sciences, Inc., directed to "Transforming Growth Factor H1"; **Document D49** (International Application No. PCT/US94/05186, filed on 10 May 1994 by Human Genome Sciences, Inc. (WO 95/19985), directed to "Hematopoietic Maturation Factor"); and **Document D50** (International Application No. PCT/US94/09484, filed on 23 August 1994, by Human Genome Sciences, Inc. (WO 96/05856), directed to "Human Chemokine Polypeptides"). All of these applications are unrelated to VEGF2 but have vast sections of descriptive text relating to recombinant DNA technology that are nearly identical (word-for-word) to sections of the opposed application.

<sup>20</sup> For example, the opposed application suggests at least the following properties and/or uses of VEGF2 (e.g., at pp. 4 and 16-17): wound healing agent, to promote growth of damaged bone and tissue and promote endothelialization, particularly where it is necessary to re-vascularize damaged tissues, or where new capillary angiogenesis is important; diagnosis of tumors; cancer therapy (also alleged as a use of VEGF2 antagonists); identify and isolate unknown receptors of VEGF2; treat full thickness wounds such as dermal ulcers, pressure sores, venous ulcers, diabetic ulcers; treat full thickness burns; plastic surgery; induce growth of damaged bone, periodontium, or ligament tissue; treatment of periodontal disease to lead to the formation of new bone and cementum with collagen fiber ingrowths; regenerating supporting tissues of teeth, including alveolar bone, cementum, and periodontal ligament; repair of cuts, particularly abdominal wounds; promotion of endothelialization in vascular graft surgery; repair damage of myocardial infarction; in vitro culturing of vascular endothelial cells; and gene therapy.

incorrect, and it is my opinion that the unsupported and widely varied activities and uses for VEGF2 alleged in the specification would be unduly burdensome for any practitioner to test.

4.6.3 Since the specification lacks any data supporting the long list of alleged properties and uses for VEGF2, I conclude that these properties and uses ascribed to VEGF2 were based wholly on speculation that VEGF2 will possess the same activities as "prior art proteins" with which "mature VEGF2" has 22-30% amino acid identity. (See opposed application at Figs. 2-3 and descriptions thereof at pp. 4-5.) However, it is my opinion that, at the time the opposed application was filed, the skilled addressee would not have considered 22-30% amino acid identity between proteins to be predictive of biological activity of the proteins.

4.6.3.1 Initially, I observe that my opinion was apparently shared by the patent examiner who prepared the International Preliminary Examination Report (**Document D51**) for the opposed application before it entered examination in Australia. In that report, the Examiner from IPEA/US observed that the description in the opposed application provides no evidence that the disclosed protein has the alleged activity, and that based upon the limited similarity to known proteins, it cannot be predicted with any expectation of success that the full length protein has the alleged activity, much less fragments, analogues and derivatives thereof.

4.6.3.2 My conclusion also is based on scientist's experiences with other "families" of proteins that share limited amino acid sequence similarity.

4.6.3.3 For example, the Transforming Growth Factor (TGF-) superfamily of proteins possess widely divergent and sometimes opposing activities. Notwithstanding widely divergent activities, members of the TGF- superfamily often share amino acid identities of 25-50% or more, *i.e.*, levels of identity that meet or exceed the identity VEGF2 shares with VEGF or PDGF- $\alpha$  or - $\beta$ .<sup>21</sup>

4.6.3.4 Insulin and Insulin-like growth factor I (IGF-1) and their respective receptors provide another example. These proteins possess significantly greater than 30% amino acid identity (*i.e.*, the level of identity between VEGF2 and VEGF), but insulin/IR are primarily involved in glucose homeostasis, whereas IGF-1/IGF-1R are primarily involved in mitogenic signaling.

4.6.3.5 Another example can be found in the proteins Epidermal Growth Factor (EGF) and Fibrillin. EGF is a growth factor that stimulates the proliferation and differentiation of many cell types, whereas fibrillin is a structural protein in microfibrils. These proteins exhibit more than 22% amino acid identity (*i.e.*, the level of identity between PDGF $\beta$  and VEGF2), but are functionally unrelated.<sup>22</sup>

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<sup>21</sup> See, *e.g.*, Document D52 (Kingsley, D., "The TGF- $\beta$  superfamily: new members, new receptors, and new genetic tests of function in different organisms," *Genes & Development*, 8:133-146 (January, 1994)); and Document D66, (Massague, J. "The transforming growth factor-beta family," *Annu. Rev. Cell. Biol.* 6: 597-641 (1990).

<sup>22</sup> See Documents D53 (Bell et al., "Human epidermal growth factor precursor: cDNA sequence, expression in vitro and gene organization." *Nucl. Acids Res.*, 14(21): 8427-8446 (1986); D54 (Genbank Accession No. X04571, EGF sequence); D55 (Corson et al., "Fibrillin Binds Calcium and Is Coded by cDNAs That Reveal a Multidomain Structure and Alternatively Spliced Exons at the 5' End." *Genomics*, 17: 476-484 (1993); D56 and D57 (Genbank Accession Nos. X63556 and L19896, fibrillin sequences).

4.6.3.6 Another example can be found in the proteins kdr receptor tyrosine kinase and c-src. Kdr, also known as VEGFR-2, is a cell surface receptor that binds VEGF and transduces the signal of this growth factor into cells that respond to VEGF. The c-src protein is not a cell surface receptor at all. These proteins exhibit more than 27% amino acid sequence identity (*i.e.*, greater than the level of identity between VEGF2 and either PDGF $\alpha$  or PDGF $\beta$ ), but are functionally unrelated.<sup>23</sup>

4.6.3.7 Another example can be found in the proteins Bcl-2 and Bax. The protein Bcl-2 (B-cell leukemia/lymphoma 2) exhibits anti-apoptotic properties through its role in such cancers as follicular lymphoma. The protein Bax is an apoptotic protein that interacts with Bcl-2 and counteracts the death repressor activity of Bcl-2. Notwithstanding their opposing activities, Bcl-2 and Bax exhibit 25% similarity at the amino acid level (*i.e.*, greater similarity than VEGF2 shares with PDGF $\alpha$  or PDGF $\beta$ ).<sup>24</sup>

4.6.3.8 Another example actually can be found in VEGF and PDGF $\alpha/\beta$ . These proteins share 21-23% amino acid similarity but have distinct biological activities.<sup>25</sup>

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<sup>23</sup> See, *e.g.*, **Documents D32, D33** (Terman et al., "Identification of the kdr tyrosine kinase as a receptor for vascular endothelial cell growth factor." *Biochem. Biophys. Res. Commun.*, 187(3):1579-1586 (September, 1992)); **D59** (Genbank Accession No. L04947 (kdr)); **D60** (Tanaka et al., "DNA Sequence Encoding the Amino-Terminal Region of the Human c-src Protein: Implications of Sequence Divergence among src-Type Kinase Oncogenes." *Mol. Cell. Biol.*, 7(5):1978-1983 (May, 1987)); and **D61** (Genbank Accession Nos. M16237, M16243-16245, and K03212-K03218, c-src sequences.)

<sup>24</sup> See, *e.g.*, **Documents D62** (Tsujimoto et al., "Analysis of the structure, transcripts, and protein products of bcl-2, the gene involved in human follicular lymphoma." *Proc. Natl. Acad. Sci (USA)*, 83:5214-5218 (July, 1986)); **D63** (Genbank Accession Nos. M13994 and M13995, Bcl-2 sequences); **D64** (Oltvai et al., "Bcl-2 Heterodimerizes In Vivo with a Conserved Homolog, Bax, That Accelerates Programmed Cell Death." *Cell*, 74:609-619 (1993)); and **D65** (Genbank Accession Nos. L22473 and L22474, Bax sequences).

<sup>25</sup> See, *e.g.*, Fig. 3 of the opposed application, and **Document D36** (column 13, lines 44-49).



4.6.4 Notwithstanding the large number of activities and uses for VEGF2 that were made in the opposed application, the applicant and inventors failed to predict what appears to be one of the most important activities of VEGF2, that of a growth factor for the lymphatic system. [See, e.g., **Document D74** (Kukk et al, 1996). Compare **Document D86** (WO 99/46364), a 1999 patent publication by the applicant for the opposed application, which teaches to use VEGF2 to treat lymphatic disorders.]<sup>26</sup>

4.6.5 To summarize, the opposed application contains no demonstration of VEGF2 activity and there is no reasonable basis upon which one skilled in the art could have predicted VEGF2 activity. For these reasons, it is my opinion that the opposed application contains an inadequate description of VEGF2 "activity," a claim limitation that is prominent in most of the claims of the opposed application.

4.7 The inadequacy in teachings related to VEGF2 biological activity is compounded by the failure to teach the first approximately 69 codons of the complete VEGF2 cDNA (i.e., the VEGF2 cDNA encoding a deduced full length VEGF2 protein of 419 residues). (See paragraphs 4.11-4.11.3, below) A molecular biologist would not have expected a partial eukaryotic polynucleotide sequence to be properly expressed in eukaryotic cells if the sequence were missing the first 69 codons.<sup>27</sup> I have carefully reviewed the patents and journal articles of the applicant HGS that were published after the opposed application and that disclose the 419 residue VEGF2 sequence. None of those publications explicitly state that the 350 residue VEGF2 or the 326 residue "mature" VEGF2 disclosed in the opposed application have been shown to possess any biological activity.

4.8 The inadequacy in teachings related to biological activity becomes compounded with respect to claims that are not restricted to VEGF2, but are directed to fragments

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<sup>26</sup> See also Jeltsch *et al.*, *Science*, 276: 1423-1425 (1997).

<sup>27</sup> All complex organisms including plants and animals and humans are comprised of eukaryotic cells. Bacteria and certain other single-cell organisms with no cellular nucleus are prokaryotic.

and/or analogues and/or derivatives of VEGF2 that possess VEGF2 activity. (See, e.g., claims 1-4, 9-15, 19-28, 34-39, 46-48, 50-54, and 56-61.) As explained in the preceding paragraphs, the description of "VEGF2 activity" *per se* is inadequate. It is a generally accepted proposition that altering proteins by changing, adding, or deleting amino acids can change or even eliminate biological activity of the native protein. Depending on the protein, the effect of any particular change may be unpredictable. Thus, one generally needs at least an activity assay (in which a protein has a demonstrated biological activity) to determine if a modified protein (such as a fragment, analog, or derivative) has retained or lost an activity of a native (unmodified) protein. However, the opposed application does not provide a single activity assay for the skilled address to employ in order to determine if fragments, analogues, or derivatives possess VEGF2 activity. Likewise, the specification as a whole fails to provide any evidence or working examples of a fragment, analogue, or derivative of VEGF2 that retains a "VEGF2 activity." Thus, there is no evidence or guidance regarding what residues are susceptible to alteration or deletion without affecting activity. Thus, the scope of the claims is broad, the ambit of the claims is indeterminate, and the field is entirely unexplored. The failure to demonstrate a VEGF2 activity and the failure to provide a VEGF2 activity assay and the suggestion that VEGF2 may have several activities (uses) place an undue burden on the part of the skilled addressee to practice the invention.

4.9 Many of the claims are sufficiently broad to embrace polypeptide molecules having no specified biological activity whatsoever. (See, e.g., at least claims 31-33, 40-45, and the claims that depend therefrom.) I have carefully reviewed the specification of the opposed application and I fail to find any indication that the applicant intended to claim polypeptides lacking biological activity. Nor do I discern an industrial applicability for such polypeptides when I read the opposed application. Thus, it is my opinion that the complete specification contains an inadequate description of the subject matter of these claims.

4.10 Many of the claims are directed to a genus of polypeptides (or to polynucleotides encoding a genus of polypeptides) defined by the ability of the polypeptides to cross-

react with antibodies that bind VEGF2. (See, *e.g.*, at least claims 16-27, 40-50, and 57-61.)<sup>28</sup> With respect to these claims, I observe the following:

4.10.1 I have carefully reviewed the specification of the opposed application and find no indication therein that the inventors intended all such polypeptides as part of the invention. In fact, the specification does not even identify this as a defining characteristic for a genus of polypeptides.

4.10.2 Moreover, neither the specification nor any of the claims specifies an activity or use for this broadly stated genus of polypeptides. In this regard, it is important to observe that these claims do not even specify a VEGF2 activity limitation. It is my opinion that many such polypeptides could be synthesized in the laboratory that would satisfy the claim limitations but that would have no useful biological activity, and no practical utility whatsoever.

4.10.3 Moreover, even though the claims attempt to define a polynucleotide (or polypeptide) invention with respect to an antibody, the specification fails to disclose (exemplify) a single antibody to VEGF2. There is no indication in the specification that any such antibodies had been made at the time that the application was filed. Nor do I find any description in the application of which portions of VEGF2 are antigenic. In other words, there is no description of the portions of VEGF2 to which antibodies would bind if VEGF2 were administered to an animal as an antigen. There is no description of studies which characterize the molecules to which VEGF2 antibodies would bind.

4.10.4 Moreover, the specification fails to disclose a single polypeptide that binds an antibody which binds VEGF2 (other than VEGF2 itself, having the

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<sup>28</sup> The claims generally also include a limitation relating to polynucleotide hybridization. As I explain elsewhere (*e.g.*, in paragraphs 2.4-2.4.3), this hybridization language fails to narrow the claims due to a lack of any limitation relating to stringency of hybridization conditions.

particular VEGF2 amino acid sequences disclosed in the application, and the admitted prior art polypeptides shown in Figure 2).

4.10.5 Moreover, the specification fails to describe any characteristics of polypeptides, other than VEGF2, that bind an antibody which binds VEGF2. The skilled addressee understands that an ability of two polypeptides to cross-react with the same antibody is indicative only of the fact that the polypeptides share a small region (epitope) of similar structure. Nothing can be concluded as to overall structural similarity or functional similarity of two polypeptides merely from the fact that a theoretical antibody can bind both polypeptides by virtue of a common epitope.

4.10.6 For these reasons, it is my opinion that the opposed application contains an inadequate description of the subject matter of claims 16-27, 40-50, and 57-61 and an inadequate description of how to use it.

4.11 Another inadequacy becomes apparent when one considers the true nature of the gene from which the VEGF2 described in the opposed application was produced. As explained in the following subparagraphs, the opposed application contains an inadequate description of the polynucleotide and polypeptide referred to as "VEGF2".

4.11.1 In my review of scientific and patent literature, I observe that at least three different research groups have published papers and/or patent applications relating to the gene from which the VEGF2 sequence of the opposed application was derived. These groups include the owner of the opposed application, Human Genome Sciences (see, *e.g.*, **Documents D43, D44-D46, and D84-D86**), Genentech (**Documents D75 and D84**),<sup>29</sup> and a group at the University of Helsinki (**Documents D71-D74**).<sup>30</sup>

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<sup>29</sup> The Genentech group calls the gene and protein VEGF related protein (VRP) instead of VEGF2.

<sup>30</sup> The Helsinki group calls the gene and mature protein VEGF-C instead of VEGF-2.

4.11.1.1 All three groups, *including the owner of the opposed application*, teach that the gene for VEGF2 encodes a protein of 419 amino acids.<sup>31</sup> The opposed application fails to teach the complete gene and protein sequence for the 419 amino acids. Rather, the opposed application teaches that VEGF2 is a polypeptide shown in Figure 1 comprising 350 amino acid residues of which approximately the first 24 amino acids represent the leader sequence which is cleaved off to yield a mature VEGF2 of 326 amino acids. (See, *e.g.*, specification at p. 4, last 8 lines; and page 5, last paragraph.) The owner of the opposed application considered the additional 69 residues to be so important that it eventually filed another patent application that re-defined the terms "VEGF2" and "mature VEGF2." (See **Document D43** at p. 7, last paragraph.) However, by virtue of the claim term "comprising," the opposed application clearly attempts to claim the entire 419 residue sequence even though it fails to disclose the entire sequence. (See opposed application at p. 29, last paragraph.)

4.11.1.2 The approximately 69 extra amino acids that are missing in the specification of the opposed application are found at the beginning of the VEGF2 molecule. As would be expected, all three groups (in their more recent publications) teach that the VEGF2 signal peptide is found at the beginning of the 419 amino acid sequence.<sup>32</sup> Thus, it would appear that the signal peptide (which is crucial for directing secretion of VEGF2 in cells) is absent from the teachings of the

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<sup>31</sup> See Documents D44-D45 (p. 7); Document D46 (p. 500, Fig. 1); Document D75 (p. 1989); Document D72 (p. 7); and Document D73 (p. 6).

<sup>32</sup> Genentech taught that the most likely cleavage was following residue 20, but suggested that cleavage might occur after residue 15 or 16. (See Document D75 at pp. 1989-1990.) Human Genome Sciences taught that 419 residue VEGF2 has putative leader sequence of approximately 23 residues such that the mature protein comprises 396 amino acids (See Document: D43 and D44 at p. 7, last paragraph). The group in Helsinki taught that 419 residue prepo-VEGF-C had a cleavage site for the signal peptide between residues 31 and 32. (See Document D71 at p. 3900.) When attempting to resolve conflicting definitions of the signal peptide, I observe that the Finnish group is the only group that published scientific evidence (amino terminal amino acid sequence) to support their definition of a signal peptide.

opposed application. The purported signal peptide taught in the opposed application actually is in the middle of the 419 residue VEGF2 molecule. (The first 24 residues of VEGF2 in the opposed application correspond to residues 70-93 of **Document D43**.)

4.11.1.3 From the published scientific literature that is available, it appears that the group from Finland that includes Kari Alitalo have performed the most detailed research regarding the VEGF2 gene and protein, which that group calls VEGF-C. [See, *e.g.*, **Documents D70, D71, and D74**.] The peer-reviewed journal publications of that group teach that the 419 residue form of VEGF2 is proteolytically processed to generate significantly smaller forms ("mature VEGF-C") having increased (enhanced and/or new) biological activities. (See **Document D71**, whole document.) For example, Dr. Alitalo's group teaches that when the 419 residue VEGF2 protein is processed by removal of more than 100 residues from the amino-terminus and removal of more than 190 residues from the carboxy-terminus, the resultant polypeptide having only about 125 of the 419 residues acquires a new ability to bind and activate a cell surface receptor known as VEGFR-2/Flk-1/Kdr; the resultant protein also shows increased affinity for binding and activating another receptor known as VEGFR-3/Flt-4.<sup>33</sup> (See, *e.g.*, **Document D71** at Fig. 10 and p. 3908, col. 2; see also **Document D73**.) Thus, it is clear from the work of others that polypeptides which could fall within the opposed application's definition of "fragment, analogue, or derivative of VEGF2" have biological activities that are different (VEGFR-2

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<sup>33</sup> It is generally accepted that circulating growth factors exert their effects on cells through receptors, such as VEGFR-2 or VEGFR-3, expressed on cell surfaces. Thus, the ability to bind and activate receptors at physiological concentrations would generally be expected to correlate with an *in vivo* biological activity.

activation) and/or more potent (VEGFR-3 activation) than VEGF2 as taught in the opposed application.<sup>34</sup>

4.11.2 For the foregoing reasons, it is my opinion that the opposed application contains an inadequate description of the VEGF2 gene and protein or of any claims broader than the partial sequences actually disclosed in Figure 1. Both the larger polynucleotide and polypeptide that are originally transcribed and translated from the VEGF2 gene and the smaller, highly active mature "VEGF-C" proteins produced by cells through transcription, translation, and processing are not described in the opposed application. The scope of the current claim set appears vastly broader than what was described:

4.11.2.1 At least claims 9-12, 30-45 use "comprising" language and might be construed to encompass the 419 residue VEGF2 protein or 419 codon VEGF2 polynucleotide that is nowhere described in the specification of the opposed application, by virtue of the fact that the applicant intends "comprising" to permit the inclusion of unstated elements, such as the approximately 69 VEGF2 codons that were never taught in the application.<sup>35</sup>

4.11.2.2 At least claims 1, 13-15, and 28 use "fragment" language and might be construed to encompass mature VEGF-C polypeptides (and polynucleotides that encode such polypeptides) discovered by others that are nowhere described in the specification of the opposed application. Similarly, at least claims 11-12, 31-35, and 40-41 recite particular portions of VEGF2 and use the term "comprising" such

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<sup>34</sup> In fact, the opposed application failed to teach any receptor for VEGF2. Moreover, since VEGF2 taught in the opposed application is missing amino-terminal sequence, it is not certain that this VEGF2 would possess any biological activity.

<sup>35</sup> Many other claims use the terms "having" or "encoding" or "encodes." If these term are interpreted in a manner analogous to "comprising," then the full scope of the corresponding claims would be inadequately described for the same reasons set forth for claims which recite "comprising."

that the patent applicant might assert that the claims include mature VEGF-C polynucleotides and polypeptides that are not described in the opposed application.

4.11.2.3 At least claims 13-18 and 34-45 define a polynucleotide or polypeptide invention to encompass polynucleotides (or encoded polypeptides) that "hybridize" to the approximately 350 codon partial VEGF2 polynucleotide sequence in the application, or to portions thereof. Such claims might be construed to encompass the 419 codon VEGF2 polynucleotide (or encoded 419 residue VEGF2 polypeptide) that is nowhere described in the specification. These claims also might be construed to encompass polynucleotides that encode mature VEGF-C or encode other polypeptides that are undisclosed. Similarly, at least claims 16-18 and 40-45 define a polynucleotide or polypeptide invention using "binds an antibody capable of binding" language. These claims, too, might be construed to encompass the 419 codon VEGF2 polynucleotide (or encoded 419 residue VEGF2 polypeptide) or the mature VEGF-C polynucleotides or polypeptides.

4.11.2.4 At least claims 2-10, 19-27, 29-30, and 46-61 depend from the foregoing claims.

4.11.3 I understand that the Australian Patent Office very recently published its intention to grant some claims in Human Genome Sciences Australian Patent Application No. 60467/96 (**Document D44**), corresponding to Acceptance Serial Number 714484. I understand that the accepted claims include claims directed to the full length (419 codon/amino acid) VEGF2 polynucleotide and polypeptide. If one of the tests for sufficiency is that further inventive ingenuity is not required to practice a claimed invention, then Human Genome Sciences seems to have pursued a patent strategy that is incompatible with the sufficiency requirement. In the opposed



application containing only a partial VEGF2 sequence, HGS has urged that it is entitled to broad claims that encompass the full-length form of VEGF2, and then in its second application, HGS has apparently urged that inventive ingenuity was required to obtain the full length VEGF2 from the partial VEGF2 in the opposed application.

- 4.12 Another inadequacy becomes apparent when one considers that the owner of the opposed application might attempt to assert the allowed claims (*e.g.*, claims 1-4, 11, 28, and 31-61) against distinct genes and proteins that the inventors of the opposed application did not discover, that no one discovered until years after the opposed application was filed, and that the opposed application provides no teaching of how to make or use.

- 4.12.1 The molecule now known as Vascular Endothelial Growth Factor-D (VEGF-D) provides a good example of the objectionable scope of the claims. The VEGF-D gene, protein, and properties are described, for example, in **Documents D67-D69**. VEGF-D is encoded by a completely different human gene than the gene that encodes VEGF2. The VEGF-D gene and protein were not known to exist at the time that the opposed VEGF2 patent was filed. The opposed application does not disclose VEGF-D, and the existence of VEGF-D could not have been known or discerned from the opposed application. However, VEGF-D is a polypeptide whose properties include certain biological activities that are the same as, or similar to, activities alleged for VEGF2 polypeptides in the opposed application. A 325 amino acid segment of VEGF-D also shares about 40 percent amino acid identity with the ~350 amino acids of VEGF2 taught in the opposed application,<sup>36</sup> and there are at least ten stretches of six identical amino acids between VEGF2 and VEGF-D which might serve as common epitopes, such that certain antibodies that bind VEGF2 would also bind VEGF-D. Under at least some hybridization conditions, one would expect the VEGF2

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<sup>36</sup> See **Document D67**, Figure 1, which contains an exemplary alignment in which VEGF2 is identified as VEGF-C (with one or two amino acid differences).

polynucleotide sequence to hybridize with the VEGF-D polynucleotide sequence.

4.12.2 To provide another example, **Document D74** discloses murine VEGF-C having about 85% amino acid identity to the protein product of the human gene corresponding to VEGF2. Murine VEGF-C shares many stretches of amino acid sequence in common with VEGF2, and one would expect that some antibodies which would bind to VEGF2 also would bind to murine VEGF-C. Likewise, the gene which encodes murine VEGF-C shares nucleotide similarity with the VEGF2 polynucleotide taught in the opposed application, so hybridization would be expected under appropriate hybridization conditions.

4.12.3 As explained in detail in the section of my declaration devoted to analysis of novelty, most claims of the opposed application are not limited to the VEGF2 sequence taught in the application. Rather, the claims attempt to define an invention with a combination of limitations directed to hybridization, antibody binding, "activity," and/or "fragment, analog, or derivatives." This language is so broad that the claims read on prior art growth factors (see paragraphs 2.2-2.8), and likewise is so broad that it reads on VEGF-D, murine VEGF-C, and other molecules that are distinct from VEGF2 and were not even discovered until years after the filing of the opposed application. Since the claims could be construed to include polypeptides that the applicant for the opposed application did not describe in the opposed application and presumably did not know existed, the scope of the claims is inadequately described.

4.13 To the extent that any features of the claimed invention are allegedly described in the Examples, I find that the opposed application to be inadequate, because the Examples contain apparent errors and omissions.

4.13.1 Example 1 of the opposed application describes Northern hybridization studies that were performed to analyze VEGF2 mRNA expression in various cells. The opposed application reports that a message of 1.6 kD was observed in Northern hybridization studies. Initially, I note that scientists do not normally report the size of mRNA in kiloDaltons (kD, a measurement of molecular weight), but rather, report such sizes in length, *e.g.*, kilobases (kb). (Compare "kD" used in specification text at p. 27 with "kb" used in Figure 5.) Next, I observe that a 1.6 kb size is inconsistent with subsequent Northern studies published by the applicant's own scientists<sup>37</sup> and by other researchers.<sup>38</sup> Third, I observe that the description of the experimental results in the text of the specification does not correspond with the results depicted in the Figure. There is no significance whatsoever ascribed to the results allegedly depicted in Figure 5. Figure 5 appears to depict hybridization of a VEGF2 probe to an mRNA species identified as 1.3 kb in size, which is inconsistent with results reported in Example 1 (Figure 4 and text) and inconsistent with other studies. Collectively, this data suggests to me that the VEGF2 probe used in the experiments reported in Example 1 of the opposed application contained sequences from a gene other than the gene which produces VEGF2, or that the Northern studies were somehow performed incorrectly.<sup>39</sup>

<sup>37</sup> See, *e.g.*, **Document D46** at Fig. 2 and p. 500 (Hu et al., "A novel regulatory function of proteolytically cleaved VEGF-2 for vascular endothelial smooth muscle cells," *FASEB J.*, 11: 498-504 (1997). This document, published by a named inventor and others at Human Genome Sciences, discloses Northern hybridization studies of VEGF2 in which a band of about 2.2-2.4 kb, and no band of 1.6 kb, was identified.) See also **Document D86** at Figures 14 & 15 and Example 8 (pp. 104-105).

<sup>38</sup> See, *e.g.*, **Document D70** at p. 292 and 296 (Fig. 7), disclosing that a probe corresponding to the gene from which the VEGF2 cDNA was derived (named VEGF-C by the authors) hybridizes to 2.4 kb and 2.0 kb mRNA species in Northern analyses, and no band of 1.6 kb. See also **Document D75** at pp. 1991-1992 and Fig. 6, disclosing that a probe corresponding to the gene from which the VEGF2 cDNA was derived (named VRP by the authors) hybridizes to a major band of about 2.4 kb and possibly a minor band of 2.2 kb in Northern hybridization studies.

<sup>39</sup> Claim 39 tries to define an invention by reference to "hybridizes to the complement of human VEGF-2 mRNA. The confusion about the identity of VEGF2 mRNA in this patent application renders claim 39 confusing, too.

- 4.13.2 Example 2 of the opposed application describes *in vitro* transcription and translation experiments, *i.e.*, attempts to generate an encoded RNA and an encoded protein from a DNA, in a test tube. The *in vitro* transcription and translation experiments, by their very nature, do not (and cannot) provide any information about VEGF2 biological activities or about the manner in which VEGF2 DNA is transcribed or translated or post-translationally-processed in living cells or organisms. The 36-38 kD and 38-40 kD polypeptides purportedly produced in Example 2 do not correspond to "mature VEGF2" as taught in the specification of the opposed application, and do not correspond in size or description to VEGF2 as later reported by the applicant<sup>40</sup> and others<sup>41</sup> in the scientific literature.
- 4.13.3 Moreover, the procedures described in Example 2 are not repeatable by a skilled addressee because the description is incomplete and inaccurate. The Example is incomplete in that the applicant used "VEGF primer F5" but failed to describe its sequence anywhere in the opposed application. The Example reports that the primer pair that includes primer F5 (the third primer pair) produced PCR products that encode the full polypeptide of VEGF2 but it is not clear from the description how the third primer pair can produce such products. The Example is scientifically inaccurate in that it states (and Figure 6 purportedly confirms) that the second primer pair produces a PCR product that "misses 36 amino acids coding sequence at the C-terminus of the VEGF2 polypeptide." This description is contrary to what should be produced by a primer pair that amplifies *the complete coding sequence plus 169 bp of additional 3' sequence*, as taught in Example 2.

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<sup>40</sup> The Hu et al. article, published by the applicant's scientists, discloses that cells produce a VEGF2 of a molecular weight significantly greater than 36-40 kD that is processed into forms that are significantly smaller than 36-40 kD. (See, Document D46 at, *e.g.*, pp. 501-502 and Figs. 3-4.)

<sup>41</sup> See Document D71 (Joukov et al.) discloses actual experiments showing that the protein product of the gene from which the VEGF2 cDNA was derived (designated VEGF-C by the authors) is expressed as polypeptides significantly greater than 36-40 kD in size and processed into polypeptides that are significantly smaller than 36-40 kD in size. (See whole document, especially Fig. 10.) See also Document D75 (Lee et al.) predicts that the protein product of the gene from which the VEGF2 cDNA was derived (designated VRP by the authors) produces a mature polypeptide of a molecular weight of 44.8 kD, *i.e.*, greater than 36-40 kD.

Such a primer pair should result in an *in vitro* product that is not missing any amino acids from either terminus. Additionally, the description of "lanes" in Fig. 6 (which purportedly depicts results from Example 2) are inconsistent with the description of lanes in the text of the specification (at page 29) that refers to Figure 6. In addition, the "FGF control" specified in Figure 6 is not described anywhere in the text of the specification.

4.13.4 As explained above in paragraphs 2.3-2.3.5, the examples contain no data relating to VEGF2 activity or how to test for it.

4.13.5 For all of these reasons, I find that the experiments described in the Examples of the opposed application are inadequately described.

4.14 In conclusion, I am of the opinion that the opposed application contains a specification which comprises: (a) large sections of "stock" text which has no particular relevance to VEGF2 (as compared to any other gene or protein of interest); (b) predictions of biological activity and uses that are not based on any apparent experimental evidence but that are based on levels of sequence homology (22-30%) that are too low for reliable prediction; and (c) examples that are incomplete, internally inconsistent, inconsistent with later published data, and that teach nothing concerning VEGF2 biological activity. These teachings are inadequate to enable the broad scope of the claims.

### **Claims Not Fairly Based**

#### **A. Introduction**

5.1 Through my involvement in this matter, it is my understanding that Australian patent law includes a "fair basis" requirement that focuses on whether an invention as claimed is commensurate with the disclosure in an application. It was explained to me that a claim whose scope goes beyond the disclosure of the description found in the specification (*i.e.*, a claim to an invention for which there is no real and reasonably clear disclosure) is not fairly based, and should not be granted. I was told that "fair basis" is a fact-specific inquiry that must be made on a case-by-case

basis and with consideration of the common general knowledge in the field(s) of the invention. However, I was told that certain guiding principles/inquiries are relevant to any fair basis analysis:

- 5.1.1 For example, one line of inquiry focuses on whether or not the alleged invention as claimed is broadly described in the specification.
- 5.1.2 Another inquiry is whether or not there is anything in the specification which is inconsistent with the alleged invention as claimed.
- 5.1.3 Another inquiry is whether or not the claim includes as a characteristic of the invention a feature as to which the specification is wholly silent.
- 5.1.4 Speculative claims that seek protection well beyond the consideration given by the specification in its description of the invention are properly objected to for lack of fair basis. (The concept of "consideration given by the specification" is a concept relating to the contribution that a patent applicant gives to the public through the novel teachings in a patent application, in exchange for patent rights that the applicant receives from the public.) This inquiry is particularly relevant when a claim is broad, the ambit of the claim is indeterminate, and the field claimed is largely unexplored.
- 5.1.5 Claims that are open-ended and so broad as to cover processes or products unrelated to the process or product actually disclosed in the specification are objectionable for lack of fair basis.
- 5.1.6 If there is some feature in a claim to which no reference is made in the body of the specification, or if a claim is not limited by its terms to what the patentee has stated in the body of the specification to be the embodiment of the invention, then the claim is objectionable for lack of fair basis.

5.2. I was asked to review the opposed application, the prosecution history, related documents published by the Applicant and others, and the state of the common general knowledge at the time of filing, with the preceding guidelines in mind, and provide a scientific analysis relevant to the question of whether or not claims in the opposed application are fairly based on the specification. My analysis above relating to insufficiency of the claims is relevant to this section, and is incorporated by reference. Additional particulars of my analysis follow.

**B. The claims of the opposed application are not fairly based on the specification**

5.3 Many claims (*e.g.*, claims 17, 19-27, 38, 46-50, and 57-61) attempt to define an invention by reference to an American Type Culture Collection (ATCC) biological deposit that is not identified anywhere in the specification.

5.3.1 I find mention of only one biological deposit in the specification of the opposed application, namely ATCC Accession No. 75698 (Plasmid 182,618) deposited on 4 March 1994. (See p. 5.) The application was originally filed with empty blanks instead of a cross-reference to a deposit. From reviewing the file history of the opposed application, I observe that the cross-reference to the ATCC 75698 deposit was added to the application by the applicant long after the filing date, with the Patent Office's permission.

5.3.2 Claims 38 and 44 (and thus claims 46-50 and 61 which depend therefrom) each specifies ATCC Deposit No. 97149, which is not described or referenced anywhere else in the opposed application.<sup>42</sup>

5.3.3 Claim 17 (and claims 19-27 and 57-60 which depend therefrom) each specifies ATCC Deposit No. 75968, which is not described or referenced anywhere else in the opposed application. (I suspect that "75968" merely

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<sup>42</sup> The American Type Culture Collection (ATCC) is a biological depository that maintains biological materials under conditions so that they remain viable and reproducible. The ATCC accords each deposit its own accession number (reference number), and 75698 and 97149 would represent separate and distinct deposits at the ATCC.

reflects a typographical error. However, the claim as it is written literally refers to some other ATCC deposit, and not the one mentioned in the specification.)

5.3.4 These claims which attempt to define an invention by reference to a biological deposit that is nowhere mentioned in the specification are a clear example of the inclusion in a claim of a feature as to which the specification is wholly silent. Thus, there is no fair basis for these claims in the opposed application.

5.4 Many claims (*e.g.*, 1-10, 13-15, 19-30, 34-39, 46-51, and 53-61) attempt to define an invention by reference to VEGF2 "activity," yet the specification as a whole fails to provide any evidence of a VEGF2 activity.

5.4.1 I repeat by cross-reference my extensive analysis of the shortcomings of the opposed application related to "activity" earlier in this declaration, *e.g.*, in paragraphs 2.3-2.3.5 and 4.6-4.8. There, I explain that the specification lacks any demonstration of VEGF2 activity, lacks any teaching of a VEGF2 activity assay, presents only a large list of speculative uses, and fails to appreciate or predict what appears to be one of the most prominent effects of the protein produced by cells that express the gene that corresponds to VEGF2 (a lymphatic growth factor effect). Moreover, because VEGF2 taught in the opposed application is missing about 69 amino-terminal residues, it is dubious whether this VEGF2 would be expressed and secreted as an active protein by eukaryotic cells.

5.4.2 Notwithstanding the dearth of teachings, the claims apparently attempt to encompass any polypeptide that possesses any VEGF2 activity. (I repeat by cross-reference my extensive analysis of claim scope in the paragraphs above relating to lack of novelty.)



5.4.3 In my opinion, these facts clearly amount to an instance of speculative claims that seek protection well beyond the consideration given by the specification in its description of the invention. The claims are exceedingly broad, and their ambit is indeterminate due to the lack of clear meaning of "VEGF2 activity" from the specification. Almost by definition, the identification and characterization of any new gene represents a venture into a field that is largely unexplored.

5.5 Many claims (*e.g.*, claims 1-4, 9-15, 19-28, 34-39, 46-48, 50-54, and 56-61) seek protective well beyond any consideration provided in the opposed application in that they attempt to define an invention pertaining to fragments and/or analogues and/or derivatives of VEGF2 that possess VEGF2 activity (or polynucleotides encoding them). As explained in the following subparagraphs, the specification as a whole fails to provide any evidence of a VEGF2 activity, fails to provide an assay to determine if fragments possess VEGF2 activity, and fails to demonstrate a single active fragment, analogue, or derivative of VEGF2.

5.5.1 Claims which embrace fragments, analogues, or derivatives embrace a virtually infinite number of polynucleotides or polypeptides, yet the specification provides essentially no guidance as to those species which will retain "VEGF2 activity" and those species which will not. In particular, there is no guidance as to what portions of the VEGF2 molecule are required for activity and what portions are not. I repeat by cross-reference the analysis in paragraph 4.8.

5.5.2 As explained in paragraphs 2.2-2.8, these claims are so broad that they encompass prior art polynucleotides and polypeptides. Moreover, the specification provides no structural basis for distinguishing an analog or derivative of VEGF2 from an analog or derivative of VEGF, PlGF, PDGF, or other VEGF-related growth factors that were known or suggested by the prior art. Likewise, the specification provides no functional basis for

distinction, since the alleged VEGF2 activities are predicted to match activities of these prior art growth factors.

5.5.3 As explained in paragraphs 4.12-4.12.3, these claims (*e.g.*, at least claims 1-4, 11, 16-20, 22-24, 28, 31, 32, 34-45, 47-48, and 53) are so broad that they potentially encompass polypeptides and polynucleotides that are derived from different genes and that were not discovered by the applicant and were not described in the specification of the opposed application. These encompassed polypeptides and polynucleotides, like VEGF2, exist in nature and owe nothing to the teaching of the alleged invention.

5.6 Many of the claims (*e.g.*, at least claims 1-4, 11, 13-20, 28, 32, 34-45, and certain claims that depend therefrom) seek protection well beyond any consideration provided in the application to the extent that they can be interpreted to read on non-human forms of the VEGF2 polynucleotide or polypeptide or uses thereof.

5.6.1 The specification provides no structural basis for distinguishing non-human forms of VEGF2 from non-human forms of VEGF, PIGF, PDGF, or other VEGF-related growth factors that are not identified in the specification but that exist in nature. Likewise, the specification provides no functional basis for distinction, since the alleged VEGF2 activities are predicted to match activities of the prior art growth factors.

5.6.2 The specification of the opposed application explicitly states that "The VEGF2 of the present invention is of human origin." (See, p. 3, last line.) No non-human VEGF2's are disclosed.

5.6.3 Nonetheless, most or all of the claims that are not specifically limited to the alleged human sequence taught in the application might be asserted to encompass non-human polynucleotides or polypeptides due to the breadth of limitations pertaining to fragments, analogues or derivatives (see, *e.g.*,

paragraphs 2.2-2.2.2, 2.7.1, and 2.7.9) hybridization (see, *e.g.*, paragraphs 2.4-2.4.3), and antibody binding (see, *e.g.*, paragraphs 2.5 and 4.10-4.10.6).

5.7 Many claims (*e.g.*, each of claims 16-18 and 40-45, and claims depending therefrom) attempt to define an invention in terms of a polypeptide which binds an antibody capable of binding to VEGF2. The following observations are relevant to a fair basis analysis of these claims:

5.7.1 I have carefully reviewed the specification of the opposed application and find no language that supports claims reciting a polypeptide which binds an antibody capable of binding to VEGF2. There is no indication that the applicant intended to define the invention in this manner. Upon reviewing the file history, I observe that none of the original claims (as they appear in the prosecution history) attempted to define the invention in this manner.

5.7.2 I analyzed the enormous scope of these claims and the shortcomings of the specification's teachings with respect to these claims extensively above (*e.g.*, in paragraphs 2.2-2.8 and 4.10-4.10.6), which I incorporate by reference. Those paragraphs explain that the indicated claims encompass prior art and other sequences which owe nothing to the teachings of the specification.

5.7.3 Other than VEGF2 itself and prior art polypeptides, the specification fails to identify any polypeptides that bind an antibody capable of binding to VEGF2, fails to identify the properties of such polypeptides, and fails to identify an industrial applicability of such polypeptides.

5.7.4 Thus, these facts amount to another instance of broad, speculative claims that seek protection well beyond the consideration given by the specification in its description of the invention.

5.8 Many claims (e.g., claims 11-12, 31-35, 40-41, and claims dependent therefrom) recite specific subsequences of the alleged VEGF2 sequences taught in the Figures or Sequence Listing. The following observations are relevant to a fair basis analysis of these claims:

5.8.1 Claims 11 and 32 define a genus of polynucleotides and a genus of polypeptides, respectively, with reference to amino acids 61-74 of SEQ ID NO: 2. Residues 61-74 of SEQ ID NO: 2 of the opposed application correspond to a sequence Pro Cys Val Ser Val Tyr Arg Cys Gly Gly Cys Cys Asn Ser. There is no mention of this specific sequence anywhere in the application. At the very bottom of page 5, the specification states that "the signature for the PDGF/VEGF family, PXCXXXXRCXGCCN, is conserved in VEGF2 (see Figure 2)." (In Figure, 2, the specified sequence is enclosed in a box.) I observe that this motif in VEGF2 corresponds to residues 60-73 of SEQ ID NO: 2, not 61-74. However, assuming for the sake of argument that the applicant intended for the claims to refer to residues 60-73, it remains my opinion that the specification evinces no intent to *claim* a genus of polypeptides using this sequence as the critical, defining limitation. The context of the quoted statement indicates that the statement is merely one of comparison of the structural-relatedness of the VEGF2 sequence to prior art sequences. There is no mention of the exact sequence *per se*, but rather, merely an observation that VEGF2 includes a segment that matches a motif (PXCXXXXRCXGCCN, where X is any amino acid). There is no more indication that the applicant intended to define a claim by this motif sequence than there is an indication that they intended to define a claim by the referent PDGF and VEGF sequences that are mentioned numerous times in the same paragraph, and that formed the original basis for discerning the motif. With respect to the known polypeptides VEGF and PDGF, I am unaware of any evidence even to this date that the specified motif sequence alone is sufficient to confer the biological activities associated with these polypeptides. It would be quite surprising to researchers in this field if this fourteen residue peptide portion

of VEGF, PDGF, or VEGF2 possessed the same biological activity as the forms of VEGF, PDGF, or VEGF2 that are truly produced in the human body, which are thought to be much larger. (See, *e.g.*, opposed application at page 2, last paragraph, stating that VEGF has four isoforms of 121, 165, 189, and 206 amino acids.)

- 5.8.2 Claim 34 defines an invention by nucleotides 323 to 364 of SEQ ID NO: 1, *i.e.*, that portion of SEQ ID NO: 1 that encodes the "signature" sequence referred to at the bottom of page 5 and boxed in Figure 2. Thus, the comments in paragraph 5.8.1 pertain equally to claim 34.
- 5.8.3 Claim 40 defines an invention by nucleotides 323 to 364 of SEQ ID NO: 1, *i.e.*, that portion of SEQ ID NO: 1 that encodes the "signature" sequence referred to at the bottom of page 5 and boxed in Figure 2. Thus, the comments in paragraph 5.8.1 pertain equally to claim 40. Moreover, the invention of claim 40 allegedly resides in any sequence that is encoded by a sequence *that hybridizes* to the indicated sequence, and that binds an antibody that binds VEGF2. As explained in paragraphs 2.4-2.5 and 4.10-4.10.6, above, these other "limitations" vastly *broaden* the scope of the claim relative to claim 32 or 34 which are themselves broad, but which do require particular short sequences. The only sequences disclosed in the opposed application that actually satisfy the limitations of claim 40 are the single VEGF2 sequence and prior art sequences such as VEGF (see paragraph 2.7.12).
- 5.8.4 Claims 12 and 33 define a genus of polynucleotides and a genus of polypeptides, respectively, with reference to amino acids 38-118 of SEQ ID NO: 2. Residues 38-118 of SEQ ID NO: 2 of the opposed application correspond to a sequence beginning Met Pro Arg Glu . . . and ending Cys Arg Cys Met. There is no mention of this specific sequence anywhere in the application. Near the bottom of page 5, the specification observes that "It is particularly important that all eight cysteines are conserved within all four

members of the family (see boxed areas of Figure 2)." I observe that these eight boxed cysteines (there are many other cysteines) begin at residue 37 of SEQ ID NO: 2 and extend to residue 117 of SEQ ID NO: 2, not 38-118. However, assuming for the sake of argument that the applicant intended for these claims to refer to residues 37-117, it remains my opinion that the specification evinces no intent to claim a genus of polypeptides by this sequence. The context of the quoted statement indicates that the statement is merely one of comparison of the structural-relatedness of the VEGF2 sequence to prior art sequences. There is only mention of the cysteines, and no mention of the intervening 70+ amino acids that are dispersed between the cysteines and that comprise most of the sequence between 37 and 117. There is no mention a particular VEGF2 fragment defined by the cysteines and including all of the residues between 37 and 117. There is no more indication that the applicant intended to define a claim by residues 38-118 (or 37-117) than there is an indication that they intended to define a claim by the referent PDGF and VEGF sequences that are mentioned as sharing the eight cysteines, and that formed the basis for discerning the existence of the cysteine motif.

5.8.5 Claim 35 defines an invention by nucleotides 254 to 496 of SEQ ID NO: 1, *i.e.*, that portion of SEQ ID NO: 1 beginning with the codon for the first conserved (boxed) cysteine and ending with the codon for the eighth conserved cysteine. Thus, the comments in the preceding paragraph pertain equally to claim 35.

5.8.6 Claim 41 defines an invention by nucleotides 254 to 496 of SEQ ID NO: 1, *i.e.*, that portion of SEQ ID NO: 1 beginning with the codon for the first conserved cysteine and ending with the codon for the eighth conserved cysteine. Thus, the comments in paragraph 5.8.4 pertain equally to claim 41. Moreover, the invention of claim 41 allegedly resides in any sequence that is encoded by a sequence that hybridizes to the indicated sequence, and that binds an antibody that binds VEGF2. As explained in paragraphs 2.4-

2.5 and 4.10-4.10.6, above, these other "limitations" vastly *broaden* the scope of the claim relative to claim 33 or 35 which are themselves broad, but which do require particular sequences. The only sequences disclosed in the opposed application that actually satisfy the limitations of claim 41 are the single VEGF2 sequence and prior art sequences such as VEGF (see paragraph 2.7.12).

- 5.8.7 Claim 31 defines a genus of polypeptides with reference to amino acids 108-121 of SEQ ID NO: 2. There is no mention of this specific sequence anywhere in the application, and thus no indication from the specification that the applicant intended to define a claim by this particular subsequence.
- 5.8.8 Thus, it is my opinion that the specification is wholly silent about features of these claims, or at least is silent in the sense that the specification failed to indicate that these features were intended as features defining the invention in any broad sense.
- 5.8.9 Moreover, these are speculative claims that seek protection well beyond the consideration given by the specification in its description of the invention. Even if we presume for argument's sake that the brief excerpts at page 5 were sufficient in a general sense to provide a description, the fact remains that there is no scientific evidence supporting the notion that the indicated subsequences (fragments) encode a polypeptide having VEGF2 activity, or that the indicated subsequences are the only sequences critical for retaining VEGF2 activity. Also, since there is no actual definition or demonstration or assay for VEGF2 activity, the opposed application fails to enable a worker possessed with the common general knowledge to test such fragments for VEGF2 activity.
- 5.8.10 Claim 39 doesn't recite a particular sequence, but instead recites "human VEGF-2 mRNA." As explained above in detail, Example 2, which provides the only arguable description of VEGF2 mRNA, apparently was performed

incorrectly, and VEGF2 mRNA was misidentified. (See, *e.g.*, paragraph 4.13.1. Published evidence indicates that the only mRNA that was characterized was not, in fact, a VEGF2 mRNA.) Thus, I find no support in the application for this term, either.

5.9 When one considers what is now known about VEGF2, it becomes apparent that all the claims of the opposed application seek to define a monopoly which goes beyond the consideration provided by the specification. The specification provides what is now known to be only a *partial* nucleic acid and deduced amino acid sequences of a 419 codon and residue VEGF2 cDNA and protein. (See, *e.g.*, paragraphs 4.11-4.11.2.4, above.) Although the specification provides speculation as to the biological activity of the encoded protein, it does not provide any demonstration of biological activity, and it failed to appreciate what appears to be the most significant activity of the protein that is naturally produced by cells that express the VEGF2 gene. (See, *e.g.*, paragraphs 2.3-2.3.5 and 4.6-4.6.5.) Further, the person skilled in the art would not have considered it appropriate to make a sound prediction as to the activity based solely on the limited extent of homology between VEGF2 and prior art proteins. (See, *e.g.*, paragraphs 4.6.3-4.6.3.8, above.) When one considers what is now known about VEGF2, it becomes apparent that the consideration provided in the specification is little more than a partial sequence with no demonstration of activity.

5.10 At least claims 1, 9-18, 28, and 30-45, and claims dependent therefrom, of the opposed application extend beyond the subject matter of the alleged invention.

5.10.1 I repeat by cross-reference my analysis in paragraphs 4.11-4.11.3, where I explain that the specification of the opposed patent teaches only the final 350 codons/residues of the complete, 419 codon/residue VEGF2 cDNA and encoded polypeptide; it fails to teach the first 69 codons/residues, including the signal sequence at the beginning which is generally recognized as necessary for eukaryotic host cells to express and secrete a protein. However, the indicated claims could be construed to encompass (a) the full



length, 419 codon/residue VEGF2 cDNA/polypeptide with the true VEGF2 signal sequence; and/or (b) mature VEGF-C proteins discovered by others that have properties distinct from the 350 amino acid VEGF2 taught in the opposed application. Thus, the indicated claims seek a monopoly which is considerably broader than the consideration provided to the public through the teachings in the specification.

- 5.11 Claims 13-27, 34-50, and 57-61, at least, are not reasonably based on the material disclosed in the specification, because these claims attempt to delimit a genus of polynucleotides (or encoded polypeptides) by an ability to "hybridize" to a referent sequence. The claims which recite hybridization language do not specify hybridization conditions, and almost any polynucleotide can be made to hybridize to a given sequence under hybridization conditions of sufficiently low stringency. Given that no hybridization conditions are specified in the claims, the claims encompass prior art sequences and other sequences that owe nothing to the teaching of the specification. I repeat by cross-reference my analysis in paragraphs 2.4-2.4.3, 2.7.4-2.7.6, 2.7.11, and 4.11-4.12.3.
- 5.12 As I explain above in sections relating to novelty and inventive step, most or all of the claims in the opposed application include within their scope subject matter that was already known to the public, or was an obvious and routine variation of what was known to the public. Subject matter which was known or obvious to the interested scientific public cannot logically form part of the consideration *given by the patent applicant* to the public for the monopoly patent right that the applicant is seeking. Thus, I conclude that claims that are not novel or inventive, by definition, seek protection beyond the consideration given to the public by the specification. Thus, I would conclude that the claims are not reasonably based on the inventors' contributions embodied in the opposed application.

#### **Lack of Clarity in the Claims**

##### **A. Introduction**

6.1 It was explained to me that Australian patent law includes a "clarity" requirement. I understand that the claims of a patent are the portion that define the invention for which a patentee receives a monopoly, and the clarity requirement is a statutory obligation to state the invention clearly and distinctly in the claims. As part of my analysis of the opposed application, I was asked to evaluate whether the claims were clear to a skilled reader. I was told that certain guiding principles are relevant to any clarity analysis, including the following:

6.1.1 that any evaluation of clarity requires reading the claims in the context of the specification as a whole. For example, the specification may define claim terminology directly or aid in understanding claim terminology. My observations below were made while being mindful of the teachings and definitions provided in the specification of the opposed application.

6.1.2 that another aspect of clarity focuses on internal consistency, *i.e.*, whether the invention defined in the claims is the same invention as that described in the specification. For example, features emphasized in the description, especially those described as critical or essential, should be included in each claim.

6.2 In my study of the opposed application and its claims, I made several observations relevant to the issue of clarity, which I set forth below.

**B. Analysis of the clarity of the claims of the opposed application.**

6.3. *Lack of Clarity issues relating to the applicant's biological deposit.* The specification of the opposed application states that the controlling definition of the VEGF2 invention resides in the DNA and deduced amino acid sequence of the VEGF-2 cDNA clone deposited by the applicant with the ATCC. (See specification, paragraph bridging pages 8-9.) The specification also states that the drawings are not meant to limit the scope of the invention as encompassed by the claims. (See p. 4.) These statements raise several confusing issues.

6.3.1 Although the specification of the opposed application (as amended during prosecution) describes only a single relevant deposit (ATCC 75698), the present claims specify at least three different ATCC Accession Numbers: 75698, 75968, and 97149. Many claims (*e.g.*, each of claims 17, 19-27, 38, 46-50, and 57-61) make reference to American Type Culture Collection (ATCC) biological deposit numbers 75968 and/or 97149 that are not mentioned anywhere in the specification. (See paragraphs 5.3-5.3.4, above.) The meaning of such cross-references is unclear to a skilled reader.

6.3.2 Notwithstanding the express teaching that the drawings are not meant to limit the invention, many claims define the invention with respect to sequences depicted in Figure 1 (see, *e.g.*, at least claims 1, 5, 7, 9, 28, 29, 56-61, and claims dependent therefrom). Many other claims define the invention with respect to sequences in SEQ ID NOs: 1 or 2 (see, *e.g.*, claims 9-13, 16, 30-37, 40-43, and claims dependent therefrom). The choice to define the invention with respect to the figures or sequence listing instead of the "controlling" deposit raises issues of clarity, at least if the sequence of the deposited clone does not match the sequences in Figure 1 and/or SEQ ID NO: 1. As explained below in greater detail, inconsistencies exist amongst these sequences.

6.3.2.1 For example, position -21 of SEQ ID NO: 2 is a lysine residue (Lys). In contrast, the same position in Figs. 1A and 2A is a leucine (Leu) residue.

6.3.2.2 For example, the sequence spanning residues 274-279 of SEQ ID NO: 2 is Lys Cys Cys Leu Leu Lys. The corresponding sequence in Figs. 1C and 2B is Lys Cys Leu Leu Lys (depicted in single letter abbreviations K C L L K). Thus, SEQ ID NO: 2 includes a Cysteine that is absent from the sequence in the Figures.

6.3.2.3 The applicant performs automated sequencing which the applicant represents may have an error rate of as high as three percent,<sup>43</sup> suggesting that perhaps as many as 45 other sequence discrepancies may exist between the ATCC deposited clone and the sequences set forth in the sequence listing and figures of the application.<sup>44</sup>

6.3.3 Since the sequence in the Sequence Listing is not identical to the sequence in the figures, it must be that the DNA and deduced amino acid sequence of the deposited clone differ from those of the sequence listing, or those in Figure 1, or both. (The sequence of the deposit cannot match two different sequences.) The inconsistencies between the "controlling" sequence in the deposit and the sequences provided in the Sequence Listing and the Figures, which are supposed to match the deposit, raise questions of clarity.

6.3.4 The inconsistencies between the sequences in Figure 1 and SEQ ID NO: 2 is particularly confusing with respect to claims 9-10 and 30, and claims dependent therefrom, because these claims make reference to both the Figures and the Sequence Listing.

6.3.5 The priority application and the Australian application as filed failed to contain a proper cross-reference to the "controlling" biological deposit. Instead, there was a blank that was filled in by the applicants during prosecution, with permission from the Patent Office. Because of the blanks, references to the biological deposit in the application *as filed* would have been uninterpretable by a skilled reader.

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<sup>43</sup> This error rate is taught in Documents D43 and D44, International Patent Application No. PCT/US96/09001 (WO 96/39515) and corresponding Australian Application No. 60467/96. This later patent application is by the same applicant as the opposed application and is also directed to "VEGF2," and it specifies that sequence accuracy is only predicted to be greater than 97%.

<sup>44</sup> The Sequence in SEQ ID NO: 1 and Fig. 1 has more than 1500 nucleotides. Three percent of 1500 is 45.

6.3.6 Also confusing is the fact that the application, as amended, specifies at least two different plasmids as allegedly corresponding to ATCC Number 75698.

6.3.6.1 In a Notice of Entitlement (**Document D76**) dated 28 January 1997, filed with the Australian Patent Office, the Applicant listed as the controlling deposit "DNA Plasmid 161,797," allegedly deposited with the ATCC International Deposit Authority on 4 March 1994 as Deposit No. 75698.

6.3.6.2 During prosecution before the Australian Patent Office, the Applicant amended page 5 of the specification to specify the same ATCC deposit number but a different plasmid, namely "the clone deposited as ATCC Accession No. 75698 (Plasmid 182,618) on 4 March 1994." (See **Document D77**.) Thus, the identity of the controlling deposit is confusing from the entirety of the record.

6.4 Most of the claims (*e.g.*, each of claims 1-10 and 13-61) define the invention using one or more of the terms "VEGF2" or "VEGF2 polypeptide" or "VEGF-2" or "VEGF-2 polypeptide" or other like variations. As explained below, these terms are unclear.

6.4.1 "VEGF2" is a term invented by the applicants for this patent application, for which there is no prior recognized meaning in the general knowledge of the art. Likewise, the specification contains no explicit definition of "VEGF2." Because VEGF2 apparently refers to a protein and a cDNA encoding it, one might expect structural (*e.g.*, nucleotide or amino acid sequence) and/or functional definition for "VEGF2," but the application is unclear on both the structural and functional attributes that uniquely define "VEGF2."

6.4.2 The specification contains no demonstration of a biological activity that is characteristic of VEGF2. (See paragraphs 2.3-2.3.5 and 4.6-4.8, above.)

Likewise, the specification contains no description or demonstration of a biological activity that is unique and defining for VEGF2. To the extent any activity is alleged for VEGF2 (or deducible from alleged uses for VEGF2), such activity matches the activities of prior art polypeptides (see paragraphs 2.3-2.3.5 and 4.6-4.8), so the activities *per se* would not serve to distinguish VEGF2 from polypeptides that had already been described by others or from polypeptides discovered by subsequent inventors that are distinct from VEGF2.<sup>45</sup>

6.4.3 There appears to be no minimum particular amino acid sequence that is deemed essential for defining a VEGF2 polypeptide, as is evident from the different minimum amino acid sequences specified, *e.g.*, in claims 31-33. The VEGF2 of claim 31 (specifying only amino acids 108-121 of SEQ ID NO: 2) theoretically has *zero* amino acids in common with the VEGF2 of claim 32 (specifying only amino acids 61-74).

6.4.4 Thus, there are no clear structural or functional features for the reader to use to determine whether or not a particular polynucleotide or polypeptide is a VEGF2.

6.4.5 The skilled artisan becomes further confounded by reading the same applicant's later patent applications that teach a different VEGF2 sequence (419 amino acids) and a different "mature VEGF2" (396 amino acids). (See **Documents D43 and D44.**)

6.5 In most of the claims (*e.g.*, each of claims 1-4, 10-15, 19-28, 34-39, 46-48, and 50-61), the concept(s) of "activity" or "biological activity" or "VEGF2 activity" is essential to the understanding of the metes and bounds of the claim. However, as explained in detail above in paragraphs 2.3-2.3.5 and 4.6-4.8, one cannot discern

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<sup>45</sup> Moreover, to the extent that biological activity is intended by the applicant as a defining characteristic, the intended distinction between VEGF2 polypeptides (*e.g.*, as recited in claim 28) and polypeptides that have VEGF2 biological activity (*e.g.*, as recited in claim 34) becomes unclear.

what is meant by "active" or "biologically active" or "biological activity" in the context of VEGF2 polypeptides and/or fragments, analogues, or derivatives thereof. There is no definition per se of VEGF2 activity. The specification contains a large list of alleged uses for VEGF2 but does not demonstrate which uses are legitimate and which are not, and does not set forth a single biological activity that would explain why VEGF2 should be efficacious for treating the entire list of maladies and conditions that are mentioned. Moreover, the specification contains no recognition of what is apparently a prominent activity of the protein produced by the gene from which the VEGF2 cDNA was derived, namely, an activity as a lymphatic growth factor.

6.5.1 The meaning of VEGF2 "activity" becomes more confused by the prosecution history. As explained above in paragraph 2.7.4, during prosecution the patent applicant argued to the Australian Patent Office that "biological activity may include immunogenic activity of the full length protein." (See Response paper dated 05 August 1998, filed by patent applicant.) Immunogenicity is *not* generally considered to be a "biological activity" of a protein, because the term "biological activity" is generally used to describe the functions of a protein in native host cells or organisms where the protein does *not* normally cause an antibody response.

6.6 In it unclear in claims 50, 52, and 56 (and claims depending therefrom) what the applicant means by the terms "antagonist" and "inhibitory activity." The concept of antagonization or inhibition of a polypeptide relates to the blocking of the biological activity of the polypeptide. Because the definition of "activity" is unclear, the definitions of "antagonist" and "inhibitory activity" cannot be ascertained.

6.7 Many of the claims (e.g., each of claims 13-27, 34-50, and 57-61) try to define the metes and bounds of the invention at least in part by hybridization terminology. The claims attempt to delimit a genus of polynucleotides (or encoded polypeptides) by an ability (or inability) of one polynucleotide to "hybridize" to a specified

polynucleotide or specified genus of polynucleotides. It is not clear what is meant in these claims by "hybridize."

6.7.1 As set forth in paragraphs 2.4 - 2.4.3, the term "hybridize" is ambiguous because it provides insufficient information to understand the relationship of two polynucleotide molecules. Under conditions of high stringency, two molecules will only hybridize if they are closely related in that their sequences are perfectly complementary or nearly so. However, under sufficiently relaxed conditions, sequences which are essentially unrelated will also hybridize to each other. None of the claims which recite "hybridize" specify the hybridization conditions, so the metes and bounds of the claims are unclear.

6.7.2 Claim 39, which tries to define an invention by reference to hybridization "to the complement of human VEGF-2 mRNA" is confusing for the reasons stated in paragraph 4.13.1, above.

6.8 *Lack of clarity with respect to method of treatment claims.* Several claims, including at least claims 51-52 and 54, are directed to methods of treating patients. There are several confusing aspects to these claims.

6.8.1 Claim 55 (and claims dependent therefrom) are ambiguous in specifying the administration of "the polypeptide of claim 15." However, claim 15 is not directed to a polypeptide at all, but rather to an isolated polynucleotide.

6.8.2 Claims 51 and 54 (and claims dependent therefrom) are ambiguous in that each apparently intends that a therapeutic amount of a polypeptide can be administered without administering any polypeptide whatsoever. In particular, claim 54 specifies that the therapeutically effective amount of polypeptide is administered by providing DNA to a patient. DNA is not a polypeptide, but a polynucleotide. Thus, even though claims 51 and 54 on their face recite administration of a polypeptide therapeutic, the applicant



apparently intends for these claims to encompass gene therapy that does not involve administering *any* of the indicated polypeptide. Thus, the meaning of "therapeutically effective amount of the polypeptide" is unclear, and apparently includes an amount equal to zero.

6.8.3 In claims 51-52 (and claims dependent therefrom), the recitations "patient having need of VEGF2" and "patient having need to inhibit VEGF2" are ambiguous. The claims appear to be an attempt to cover any medical use of a protein for which no viable medical uses have been shown by the applicant. Instead of specifying a method of treating a patient afflicted with a particular condition or specifying treatment to achieve a certain medical goal (such as amelioration of the condition), the claims set forth an ambiguity: administer to any patient in need of a substance a therapeutically effective amount of the substance. It remains unclear which patients need VEGF2, or when they need VEGF2, or how to determine how much VEGF2 they need.

6.8.4 For the same reason, the recitation in the claims of "a therapeutically effective amount" is vague and indefinite. One cannot ascertain a therapeutically effective amount when the therapeutic purpose and desired therapeutic outcome are unspecified.

6.9 As explained above (*e.g.*, in paragraphs 4.11-4.11.2.1), the opposed application does not describe a full length VEGF2, yet many claims might be said to encompass full-length VEGF2. With other claims, it is somewhat unclear exactly what the applicant intends to cover. For example, claim 1 recites "a VEGF2 polypeptide having the deduced amino acid sequence of Figure 1" and claim 29 contains a similar recitation. It is unclear whether this term is meant to limit the claims to a VEGF2 having only the amino acid sequence that is specifically recited and shown in Figure 1, or whether a VEGF2 having the sequence shown in Figure 1, plus additional VEGF2 sequence (or unrelated sequence) that was not taught in the opposed application, would also be encompassed.

- 6.10 Many claims (*e.g.*, claims 16-27, 34-50, and 57-61) try to delimit the invention with terms such as "a polypeptide which binds an antibody capable of binding to VEGF2." This terminology is ambiguous, because antibody-polypeptide interactions are not all-or-nothing interactions. Rather, such interactions are characterized by levels of specificity for a particular antigen, or by quantitative measurements of affinity, for example. There is no indication whether the claims are intended to encompass polypeptides that weakly cross-react with antibodies raised to VEGF2, or for that matter encompass situations where an antibody strongly binds to a different polypeptide (such as VEGF, or PDGF, or BR3P) and weakly cross-reacts with VEGF2.
- 6.11 Many claims in the opposed application use the term "isolated." This term would normally be clearly understood to reflect the separation of a particular item from amongst other items. However, the specification of the opposed application provides its own, somewhat broader definition: "The term 'isolated' means that the material is removed from its original environment (*e.g.*, the natural environment if it is naturally occurring). For example, a naturally-occurring polynucleotide or polypeptide present in a living animal is not isolated, but the same polynucleotide or DNA or polypeptide, separated from some or all of the coexisting materials in the natural system, is isolated. Such polynucleotide could be part of a vector and/or such polynucleotide or polypeptide could be part of a composition, and still be isolated in that such vector or composition is not part of its natural environment." (Specification at page 10, middle paragraph.) Thus, the definition of "isolated polynucleotide" or "isolated polypeptide" in the opposed application technically could embrace, for example, blood, serum, or tissue samples that are removed from a living organism, or cultured cell lines, which are separated from some or all of the coexisting materials in the natural system (the host organism). Likewise, the definition of "isolated" would appear to embrace an entire cDNA library that includes a VEGF2 cDNA in admixture with other cDNAs representing all other genes expressed in a cell or tissue. The VEGF2 cDNA in such a library is not "isolated" from the other cDNAs, but it is separated from some or all of the

coexisting materials in the natural system from which the library was derived. Thus, it is possible that the patent applicant intends "isolated" to have a broader meaning than scientists would ordinarily attribute to the term.

### **Not a Manner of Manufacture**

#### **A. Introduction**

- 7.1 As a result of my involvement in this matter it is my understanding that, under Australian Patent Law, a valid patent may not be granted for an alleged invention where the specification describes as the invention that which encompasses what is already known and referred to in the specification or where the specification merely describes an alleged invention in terms of a known and desired goal, without describing how that goal may be attained.

#### **B. Analysis**

- 7.2 In my opinion, the alleged invention as claimed in claims 1-5, 9-15, 19-28, 34-39, 46-48, 50-54, and 56-61, at least, of the opposed application was not the first disclosure of the subject matter of the opposed application. This is clear from the description provided in the specification itself. In addition to my discussion in the following sub-paragraphs I repeat by cross-reference my discussion in paragraph 2.7 and sub-paragraphs thereto.
- 7.3 In my opinion the claims of the opposed application include the polynucleotide sequence of VEGF2 and the encoded VEGF2 protein together with any biological activity of that protein. However, in describing a polynucleotide sequence which encodes a VEGF2 polypeptide, but without providing any demonstration of the biological activity of that encoded polypeptide, it is my opinion that the opposed application provides nothing more than a mere chemical curiosity.
- 7.3.1 The specification describes at page 5, lines 22 to 24, that the polynucleotide of the invention was "discovered" in a cDNA library derived from early stage human embryo week 9. The polynucleotide sequence was determined, and the encoded amino acid sequence was deduced and shown to have

homology to three known growth factor proteins (page 5, lines 24 to 30). The "highest homology" exhibited by the "protein" encoded by the polynucleotide of the alleged invention was 30% amino acid identity with VEGF. The specification states that the protein also exhibited homology to PDGF $\alpha$  (23%) and to PDGF $\beta$  (22%). On the basis of this homology the encoded polypeptide was speculated to have certain biological activity.

7.3.2 As at March 1994 (which I understand to be the alleged priority date of the opposed application), I would not have considered, and still to this day do not consider 22% to 30% amino acid identity between proteins to be soundly predictive of the biological activity of proteins either in a general sense or specifically in relation to growth factors or specifically in relation to the particular growth factors with which the opposed application is concerned. In my opinion, therefore, the degree of amino acid sequence identity between the subject sequence of the opposed application and the prior art growth factors is used merely for the purpose of unjustified speculation as to the nature of the biological activity of the polypeptide of the opposed application. The opposed application provides no evidence that convinces me that any polypeptide disclosed therein, much less any fragment, analogue, or derivative of that polypeptide, has the asserted biological activity. As further support of my opinion that the opposed application is directed to a mere chemical curiosity I incorporate by reference my discussion at paragraphs 2.3 and 4.6 and sub-paragraphs thereto.

7.4 Claims 1-5, 9-15, 19-28, 34-39, 46-48, 50-54, and 56-61, at least, are directed to an active fragment, analogue or derivative of VEGF2, and or to a polynucleotide encoding an active fragment, analogue or derivative of VEGF2. The opposed application speculates as to the nature of the biological activity of the VEGF2 polypeptide. However, there is no demonstration of VEGF2 biological activity in the specification and I have already stated that I believe the basis upon which the inventors speculate as to the nature of the biological activity is not sound.

Therefore, in so far as the claims of the opposed application are notionally limited by reference to biological activity or the requirement that the polypeptide be active I believe that they are directed merely to a desired goal.

7.4.1 This must be said to be the case even more so in respect of the claims directed to fragments, analogues, or derivatives of the disclosed sequence. In my opinion claims 1-5, 9-15, 19-28, 34-39, 46-48, 50-54, and 56-61 of the opposed application define an invention pertaining to fragments and/or analogues and/or derivatives of VEGF2 that possess VEGF2 activity, or the polynucleotides that encode such fragments, analogues or derivatives. However, the specification provides no demonstration or evidence of fragments, analogues or derivatives having VEGF2 activity as I explain in detail in paragraphs 4.6 to 4.8 and sub-paragraphs thereto.

7.5 Claims 51, 52 and 54 of the opposed application are directed to methods of treatment which utilise the polypeptide(s) or polynucleotide(s) of the opposed application. In addition to my discussion in paragraph 7.4 and sub-paragraphs thereto, I believe that these claims are directed to mere known and desired goals as illustrated by the fact that the specification contains no activity assay or activity demonstration (see paragraphs 2.3 and 4.6, and sub-paragraphs thereto, above).

7.6 The opposed application teaches that VEGF2 is a polypeptide shown in Figure 1 comprising 350 amino acid residues of which approximately the first 24 amino acids represent the leader sequence which is cleaved off to yield a mature VEGF2 of 326 amino acids (see, *e.g.*, specification at page 4, last 8 lines, and page 5, last paragraph). I refer to my discussion of paragraph 4.11 and sub-paragraphs thereto wherein I state that VEGF2 as described in the opposed application is known to be missing 69 amino acid residues at the beginning of the molecule. In my opinion this means that VEGF2 as taught in the opposed application lacks a true signal peptide and so would not be expressed and secreted by eukaryotic host cells in the manner alleged in the opposed application. The opposed application contains no evidence or successful expression and secretion from a cell, or even any attempt to

do so. Accordingly, as VEGF2 as taught in the opposed application is neither demonstrated to possess biological activity nor is likely, in my opinion, to be capable of expression and secretion from a host cell, it represents nothing more than a mere chemical curiosity as it is unlikely to be useful for expression and secretion without significant further development. I repeat by cross-reference my discussion of paragraphs 4.7 and 4.11, above, and sub-paragraphs thereto.

### Summarizing Remarks

- 8.1 It may be helpful for me to distill the foregoing analysis into a few summarizing remarks.
- 8.2 In terms of its contribution to the public knowledge, the opposed application can, at best, be said to provide a previously undescribed sequence of nucleotides from the human genome. Beyond the new sequence, most of the opposed application appears to be "stock" text that the applicant, HGS, used in many recombinant DNA patent applications during the relevant time period, irrespective of the type of DNA (or encoded protein) that was being claimed.
- 8.3 There are several noteworthy details to the VEGF2 invention that are *absent* from the opposed application, *i.e.*, that were *not* provided to the public.
  - 8.3.1 First and foremost, it is clear with the benefit of hindsight that the sequence provided in the opposed application is not even a complete VEGF2 sequence. The sequence provided is missing about 69 upstream codons, including the VEGF2 signal sequence.
  - 8.3.2 In addition to providing a sequence that is incomplete, the opposed application has internal, unexplained inconsistencies between the partial VEGF2 sequences in its Figure, its Sequence Listing, and its biological deposit.

8.3.3 The opposed application fails to provide a VEGF2 activity assay or provide any evidence of a VEGF2 biological activity.

8.4 The patent applicant has sought extremely broad patent protection notwithstanding the limited nature of the disclosure to the public.

8.4.1 Notwithstanding the teaching of only a partial VEGF2 sequence, the applicant seeks patent protection using "comprising" claims that would encompass a full length VEGF2 sequence that the applicant considers to be an invention that is separately patentable in its own right.

8.4.2 Notwithstanding the teaching of only a partial VEGF2 sequence and the failure to teach a definitive VEGF2 biological activity or VEGF2 biological activity assay, the applicant seeks protection for "hybridizing" polynucleotides (and encoded polypeptides) and any polypeptides that bind antibodies that bind VEGF2 and that possess VEGF2 activity or inhibit VEGF2 activity. The relevant claims are so broad that they encompass prior art growth factor polynucleotides and polypeptides (or obvious variants thereof), and might be asserted to encompass growth factor polynucleotide and polypeptide discoveries of others that are separate and distinct from the partial VEGF2 taught in the opposed application.

8.4.3. Notwithstanding the failure to characterize VEGF2 biological activity or its functions in the human body, the applicants have claimed therapeutic regimens that involve administering VEGF2 to patients "in need of VEGF2" and administering VEGF2 inhibitors to patients "having need to inhibit VEGF2."

AND I MAKE this solemn declaration by virtue of the Statutory Declarations Act 1959, and subject to the penalties provided by that Act for the making of false statements in

statutory declarations, conscientiously believing the statements contained in this declaration to be true in every particular.

**DECLARED** at Melbourne

this 16<sup>th</sup> day of February 2000

  
Peter Adrian Walton Rogers

BEFORE ME:

Elizabeth Kennedy

**ELIZABETH KENNEDY**

B.A. LL.B (Hons) LL.M (Melb) SOLICITOR  
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DAVID ST. DANDENONG

A natural person who is a current practitioner  
within the meaning of the Legal Practice Act 1996.



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